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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1952

ORIGINAL ARTICLES

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA

XIV. Intrinsic Factor Activity of Desiccated and Defatted Human Fundus, Duodenum, and Jejunum*

By Erik Landboe-Christensen, M.D.†
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and
William B. Castle, M.D.***

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Since the observation[6] was reported that normal human gastric juice contains a principle, the so-called gastric (intrinsic) factor, that is hematopoietically effective in pernicious anemia when administered with a source of so-called food (extrinsic) factor such as beef muscle, several contributions have been made concerning the site of production of the intrinsic factor within the gastrointestinal tract of animals and of man. An anti-anemic effect in pernicious anemia, presumably dependent on the presence of both factors[2-5,7,28a], has been demonstrated to follow the administration of preparations not only of hog stomach[2,4,7,20a,b,25,26,28a,31] but also of duodenum[2,3,8,20c,25,27], ileum[8,29], and even colon[23]. However, certain evidence[7,18,22] renders it unclear that in man extragastric sources of intrinsic factor exist. Consequently, the view has been advanced that the anti-anemic activity of the hog intestine might be due either to a different site of secretion in this species or to the passive adsorption of gastric secretion[8]. Meulengracht has proposed[20e] that this activity might represent the accumulation in the intestinal mucosa of a hematopoietic product intermediate in thermolability between intrinsic

* The expenses of this investigation were defrayed in part by the J. K. Lilly Gift to the Harvard Medical School.

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factor and the active principle in liver.

The results obtained with material from the human stomach have demonstrated the significant hematopoietic activity of preparations made with desiccated and defatted fundus[10,16a,b]. Moderate activity of similar preparations from the human pylorus[10,16b] has also been observed. No data exist on the hematopoietic effectiveness of human duodenal tissue or of the rest of the small intestine. Consequently preparations were made from human (1) fundus, (2) pylorus, (3) Brunner gland-containing region of the duodenum, and (4) proximal jejunum. Thereafter these preparations were employed in therapeutic tests in cases of untreated pernicious anemia.

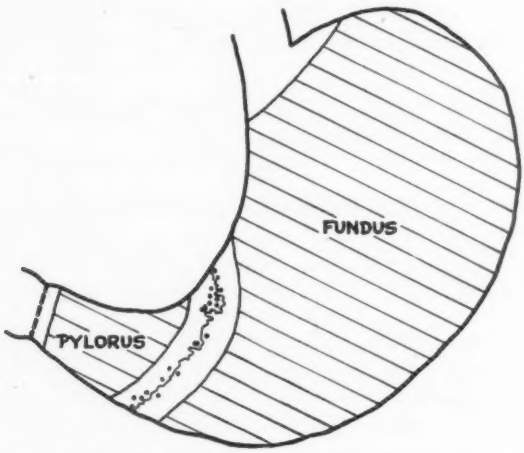

FIG. 1.—Position of the pyloric-fundal gland border in the human stomach[14]. The shaded areas indicate the "pylorus" and "fundus" portions used in the therapeutic tests.

Methods. The specimens of stomach and small intestine were obtained at autopsies on males and females ranging in age from 6 to 83, but mainly between 40 and 70 years. The cause of death was usually some cardiac or cerebral lesion and, in a few cases, pulmonary embolism or suicide. Patients with symptoms, signs, or autopsy findings of acute or chronic infections were rigorously excluded. The specimens were obtained 3 to 24 hours, commonly within 12 to 14 hours, after death. After removal of subserous adipose tissue the organs were cut open and the portions required were separated. The stomachs were opened along the greater curvature and divided into "pylorus" and "fundus" portions[14], as shown in Fig. 1. The duodenums were opened along the anterior wall and a portion was cut out from just beyond the pylorus to a little below the inlet of the bile duct, as shown in Fig. 2. This contained the bulk of the Brunner gland islands[13]. The portion of jejunum used extended from 10 cm. beyond the duodenojejunal flexure for 20 to 30 cm. distally.

After separation of the various specimens, the mucous membrane was carefully washed with running cold tap water for 1 to 2 minutes, in order to remove gastric and intestinal contents and as much as possible of the mucus covering the surface. The approximate wet weights of the specimens were: fundus 100; pylorus 20; duodenum 22; and jejunum 100 gm. Each was finely ground together with an equal weight of lean beef muscle as a source of so-called food (extrinsic) factor. This mixture was then spread out in a film 2 to 5 mm. thick on flat pans placed in a screened box and exposed to a current of air from an electric fan at room temperature for 48 hours. While drying, the surface film was broken up 2 or 3 times. The dried material was then crushed into small

pieces, defatted in 3 changes of ether, and finally placed in a desiccator for 3 to 4 days. Thereafter the material was pulverized in a mill and stored in dark stoppered bottles until required for use. The resulting powder was grayish-white, had a slightly aromatic odor, and weighed a little less than one-fifth of the original wet weight of the preparation.

The hematopoietic activity of these preparations was satisfactorily studied in 4 patients with addisonian pernicious anemia either in relapse or without previous treatment. In each, the diagnosis was established on the basis of characteristic blood and bone marrow, histamine-fast gastric anacidity, and an eventual hematopoietic response either to certain of the orally administered test preparations or to a commercial preparation of desiccated and defatted hog stomach (Ventriculin). After an initial control period, each preparation to be tested was given in 3 divided doses daily. Because possible contact with minimal amounts of food (extrinsic) factor (vitamin B_{12}) in the patients' diet would probably not substantially alter the results of a test for intrinsic factor employing preparations containing extrinsic factor, the test preparations were conveniently given immediately before meals. However, while

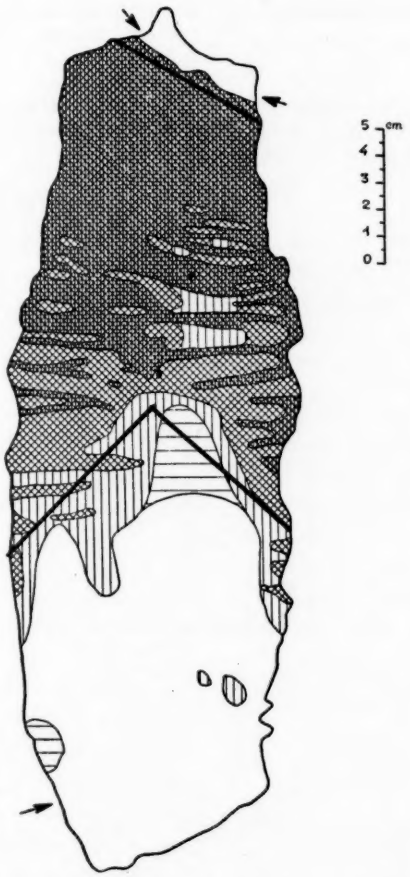

FIG. 2.—Extent and density of the Brunner gland area in the human duodenum (male, 32 years old)[13].

The two black spots indicate the duodenal papillae; the arrows, the pyloric ring and the beginning of the mesentery; and the solid black lines, the incisions employed in making the "duodenum" preparations used in the therapeutic tests.

under observation the patients received a diet containing no meat, fish or eggs, and little milk. Conventional methods involving frequent examinations of venous blood and daily reticulocyte counts were employed. Interpretation of the results was based on the method of serial reticulocyte responses during successive contiguous periods of 10 or more days of uniform daily administration of the test substances[21]. Because of the limited amounts of some of the preparations available, exceptions to this ideal procedure were required as indicated below. Transfusions were given to 3 of the patients because of low initial blood values. In our experience on numerous occasions this procedure has never led to a detectable reticulocyte response under the controlled dietary conditions employed.

Results. The hematologic results obtained in the 4 patients studied, Cases 126, 127, 128, and 129, are shown in Table 1.

Case Reports. CASE 126 achieved an initial red cell count of 1.80 million per c.mm. as a result of 2 transfusions of 500 cc. of citrated blood given during the preceding control period. During the first 5 days of the first period he was given 40 gm. of duodenum powder daily; from the 6th to the 15th day he was given no therapy. A reticulocyte peak of 4.9% was reached on the 10th day. During the first 5 days of the second period the patient received 40 gm. of fundus powder daily; from the 6th to the 12th day he received no therapy. A second reticulocyte peak of 4.3% was reached

TABLE 1.—HEMATOPOIETIC EFFECT OF THE ADMINISTRATION OF DESICCATED AND DEFATTED MIXTURES OF HUMAN FUNDUS, DUODENUM AND JEJUNUM WITH AN EQUAL WEIGHT OF BEEF MUSCLE

	Case 126		*Case 127*		*Case 128*		*Case 129*	
Days of Treatment	*R.B.C. mils.*	*Retic.** *%*	*R.B.C. mils.*	*Retic.** *%*	*R.B.C. mils.*	*Retic.** *%*	*R.B.C. mils.*	*Retic.** *%*
First periods: Daily† oral administration of substances indicated below:								
	Duodenum preparation 40 gm. (5 days)		*Duodenum preparation 18 gm. (10 days)*		*Jejunum preparation 40 gm. (9 days)*		*Jejunum preparation 40 gm. (4 days)*	
0	1.80	0.6	1.45	2.8	1.32	0.4	1.29	0.2
2	1.33	1.2	1.31	3.0	1.36	0.4	1.39	0.5
4	1.68	0.8	1.14	2.6	1.26	0.4	1.72	0.2
6	1.70	0.6	1.28	1.3	1.78‡	0.2	1.82	0.4
8	1.62	2.0	1.36	3.0	1.62	0.6	1.72	0.4
10	1.58	**4.9**	1.22	**9.6**	1.39	0.4	1.73	0.5
12	1.62	2.4	1.18	5.9				
14	1.50	1.1	1.29	3.3				
Second periods: Daily† oral administration of substances indicated below:								
	Fundus preparation 40 gm. (5 days)				*Fundus preparation 40 gm. (9 days)*		*Fundus preparation 40 gm. (4 days)*	
2	1.59	0.4			1.43	0.6	1.70	0.2
4	1.87	0.8			1.72	0.4	1.77	0.3
6	1.90	1.5			1.50	2.5	1.72	2.9
8	1.96	2.5			1.76	11.9	1.98	7.8
10	2.34	**4.3**			2.14	**14.9**	2.25	**15.8**
12	2.21	1.7			2.12	12.8		4.4
14	2.28	0.8				9.2		

* Figures in bold face type indicate peak reticulocyte values.

† Duration of period of daily administration of preparation is indicated at head of each column of figures.

‡ After transfusion of 500 cc. of blood.

on the 10th day from an initial red cell count of 1.59 million per c.mm. During a third period (not shown in Table 1) the daily administration of 40 gm. of Ventriculin for 5 days failed to cause another reticulocyte response.

CASE 127 achieved an initial red cell count of 1.45 million per c.mm. as a result of a transfusion of 500 cc. of citrated blood. He was then given 18 gm. of duodenum powder daily for the first 10 of the 14 days of the first period. On the 10th day a reticulocyte peak of 9.6% was reached. Owing to lack of cooperation it was impossible to administer fundus powder during the second period and the patient was given 30 U.S.P. units of Liver Injection daily, with a striking hematopoietic response (not shown in Table 1).

CASE 128 received 40 gm. of jejunum powder daily for the first 9 days of the first period without showing a significant rise in reticulocytes. Three days later, when the second period began, the patient received daily for 9 days 40 gm. of fundus powder, to which he responded with a reticulocyte peak of 14.9% on the 10th day from an initial red cell level of 1.43 million per c.mm.

CASE 129 achieved an initial red cell count of 1.29 million red cells as a result of a transfusion of 500 cc. of citrated blood during the control period. During the first 4 days of the first period the patient received 40 gm. of jejunum powder daily. No significant rise in reticulocytes appeared during the entire 10 days of this period. During the first 4 days of the second period the patient received 40 gm. of fundus powder daily. A reticulocyte peak of 15.8% appeared on the 10th day of this period from an initial red cell level of 1.70 million per c.mm.

In another patient the administration of 40 gm. of pylorus powder daily for 4 days failed to cause a significant reticulocyte response within 10 days. At this time it became necessary to treat the patient actively with Liver Injection U.S.P. Consequently, without subsequent evidence of ability to respond to an orally administered preparation no certain conclusion can be drawn.

Discussion. The findings in Case 126, treated with the duodenum powder, suggest that the preparation was weakly active. This is confirmed by the more definite response observed in Case 127. However, because of the interval of several days occurring between the end of the period of administration of the duodenum powder and the beginning of the period of administration of the fundus preparation in Case 126, it is not certain that the latter is the more active[21]. The results in Cases 128 and 129 give no evidence of activity for the jejunum preparation, although these patients responded readily to the subsequent administration of the fundus preparation. Cases 126, 128, and 129 testify to the consistent activity of the fundus preparation as previously reported[10,16a,b]. It is possible, but not proven, that the failure of a fifth patient to respond to the pylorus preparation resulted from the relatively weak activity of this portion of the human stomach as previously noted[10,16b].

These observations were conducted before vitamin B_{12} was available. Beef muscle, now known to contain vitamin B_{12} as the probable basis of its potentiation as extrinsic factor with gastric juice[1-3,11,12,28b], was added to the stomach and intestinal specimens in corresponding amounts before desiccation and defatting. This was done in an effort to render the amount of intrinsic factor present the limiting element in the hematopoietic potency of the combinations. Several previous observations indicate that neither the added beef muscle nor the various specimens of mucosa in the amounts given contained sufficient extrinsic factor (vitamin B_{12}) to effect significant hematopoietic responses without the aid of intrinsic factor. Thus, the maximal daily dose of the final preparations (40 gm.) corresponded to an original wet weight of about 100 gm. of beef muscle and of about 100 gm. of stomach or intestine. The daily administration of 200 gm. of beef muscle[4,7], or of 200 gm. of acid incubated or boiled[4,7] hog stomach mucosa, or of 100 gm. of hog duodenum and upper intestinal mucosa, heated to 70 to 80°C. for half an hour[5]

has been shown to be hematopoietically ineffective in other patients. However, the addition of normal human gastric juice restores the hematopoietic activity of such inactivated stomach preparations[4]. Meulengracht[20e] found that 90 gm. wet weight of heated hog jejunum, and Bethell and associates[2] that 40 gm. dry weight of heated Ventriculin, given daily resulted in small reticulocyte responses. According to Bethell's recent report[3], 40 gm. of Ventriculin would contain about 1.08 mcgm., and 40 gm. of dried hog duodenum about 11.4 mcgm., of vitamin B_{12}. Such amounts of pure vitamin B_{12} are rarely effective in pernicious anemia on daily oral administration without intrinsic factor. Consequently, unless a much larger amount of vitamin B_{12} was present in the human fundus and duodenum preparations than in these regions of the hog's alimentary tract, the positive effect of the human tissues noted here must indicate the presence of intrinsic factor. Clearly, the negative results with the human jejunum preparation indicate that there is no unusual amount of vitamin B_{12} in this particular human tissue and that in man the jejunum is not a site of intrinsic factor production. Again the findings are in contrast to the reports of Uotila[29] and of Dexter[8] for the ileum, and of Schemensky[23] for the colon, of the hog.

Whether the moderate anti-anemic potency of desiccated, defatted human duodenum indicates it as a site of secretion of intrinsic factor or whether, as suggested for the hog intestine, this potency is due to passive adsorption[8] or to active absorption[20e] of the factor secreted in the stomach is not possible to deduce from the present observations. As to passive adsorption, it was not found possible to activate the fundus of the hog's stomach by allowing surface contact with pyloric or fundal secretions during a period of 24 hours after removal of the organ[10]. The finding of hematopoietic activity in secretions collected from isolated duodenal and pyloric pouches in the hog indicates that the duodenum and the pylorus in this animal are without question sites of intrinsic factor production[15,17]. Observations on the hog, however, may not be directly applicable to man, as is clearly seen from the difference in the hematopoietic activity of preparations of the fundus of the human[10,16a,b] and of the hog[10,20a,b,28a] stomach. Although separated by an interval of no more than 20 to 30 cm., the significant difference between the hematopoietic activity of the human jejunum and duodenum preparations does not serve to distinguish active or passive absorption from actual production of intrinsic factor by the duodenum in man. However, what indirect evidence is available favors the human stomach as the major if not the exclusive site of intrinsic factor secretion. Thus, in the human disease pernicious anemia, the fundus of the stomach and not the pyloric region or the duodenum is the site of the typical degenerative process[9,19,20d,30]. Several instances of total gastrectomy have been followed by the development of pernicious anemia when the patient has survived for more than 3 years[18]. Duodenal contents of one such patient did not appear to contain intrinsic factor[22] although the ability of the test patient subsequently to respond to a known source of intrinsic factor was not established. Finally, the fact that the daily oral administration of as little as 10 cc. of normal human gastric juice with 5 mcgm. of vitamin B_{12} may produce detectable hematopoietic effects in pernicious anemia[24] adds significance to the negative results of the daily administration with beef

muscle of 75 cc. of duodenal contents from a normal individual in whom gastric secretion had been excluded by obstruction of the pylorus by a balloon[7].

Summary and Conclusions. 1. Sections were made of the wall of the fundal area of the human stomach, of the Brunner gland-containing region of the duodenum, and of the neighboring part of the small intestine (jejunum). These tissues were mixed with an equal weight of beef muscle, and were then desiccated, defatted, and pulverized.

2. Satisfactory clinical tests of the therapeutic activity of these preparations were carried out in 4 patients with addisonian pernicious anemia.

3. In the dosages employed, the duodenum preparation caused a moderate response in 2 patients. The jejunum preparation caused no response in 2 patients, in each of whom subsequent treatment with the fundus preparation resulted in a definite hematopoietic response.

4. The positive hematopoietic responses are believed to indicate the presence of so-called intrinsic factor. In the case of the duodenum preparation, passive adsorption or active absorption of gastric intrinsic factor by the tissue cannot be finally excluded.

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TREATMENT OF SPRUE WITH FOLINIC ACID: REPORT OF NINE CASES†

By Calixto A. Romero, M.D.*

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AND

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With the isolation and synthesis of pure hemopoietic substances in the last decade, new avenues for the study of the anemias have been opened. Many laboratory and clinical investigators are endeavoring to determine the exact role of these substances in the complex biochemical processes that have to do with blood formation. It appears certain that through the combined effort of these workers the precise determining factors in the pathogenesis of the various megaloblastic anemias will be recognized. Specific therapeutic agents or combinations of these will then be available for more effective clinical use. Significant accomplishments in the field of preventive medicine will inevitably follow, particularly in those areas where sprue and the nutritional macrocytic anemias are prevalent.

The isolation of hitherto unrecognized substances with hemopoietic potentialities should be of interest to clinical and laboratory investigators alike. From the practical clinical viewpoint, one should like to find out whether a new hematinic is inferior, equal, or superior to the other hemopoietic substances in general use for the treatment of one or more of the macrocytic anemias. Even if such a new agent were proven inferior to other hematinics, it deserves extensive clinical trial alone or in combination with other substances, in order to help clarify the relationship of the various pure hemopoietic agents to one another. The integration of such fragmentary data will, in the final analysis, yield valuable information for the better understanding of the pathogenesis of the anemias.

Folinic acid is an active principle isolated from enzymatic digests of liver in 1949 by Bond, Bardos, Sibley and Shive[1]. It was shown to be 10 to 100 times more active than folic acid in overcoming the inhibition of certain bacteria, caused by folic acid antagonists. This active principle appears to be identical with a factor, present in varying concentrations in commercial liver extracts, which was shown to be necessary for the growth of the microorganism *Leuconostoc citrovorum* by Sauberlich and Baumann[12] in 1948.

Laboratory investigators have worked intensively to elucidate the

† Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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biological properties and chemical nature of folinic acid or citrovorum factor. A functional and structural relationship between citrovorum factor or folinic acid, and folic acid has been demonstrated by several workers[2,3,5]. Late in 1950, Brockman and co-workers[2] described the synthesis and isolation in crystalline form of a substance which appeared to have the same biological properties as citrovorum factor.

The first clinical report of the use of folinic acid or citrovorum factor was that of Spies and co-workers[14] in December, 1950. They presented a bird's-eye view of the therapeutic activity of these agents in an assorted group of 12 patients having pernicious anemia, sprue or nutritional macrocytic anemia. Six patients responded well to massive doses of citrovorum factor equivalent to about 2 million daily units of folinic acid, administered parenterally for 10 days. The remaining 6 patients received 200 units of folinic acid daily for 10 days. Two of these showed very slight hematologic and clinical improvement. The other 4 patients did not respond at all to this dosage schedule.

Subsequent reports have dealt with the use of citrovorum factor in pernicious anemia[4,6,10] and in megaloblastic anemia of infancy[17]. In both of these conditions the hemopoietic activity of citrovorum factor is similar to that of folic acid. In experimentally induced megaloblastic anemia in monkeys, folinic acid was found to be qualitatively and quantitatively superior to folic acid as a therapeutic agent[9]. More recently, Suárez, Martinez and Suárez[15] have obtained satisfactory clinical and hematologic remissions in 2 sprue patients treated with very large daily parenteral doses.

In view of the paucity of reports of the use of citrovorum factor or folinic acid in sprue, we have selected a group of these patients and observed closely their clinical and hematologic response to intramuscular folinic acid.*

Material and Methods. Nine cases of sprue are the subject of this report. The symptoms and findings in this group of patients parallel those of 100 cases of sprue carefully analyzed by Rodriguez-Molina at the School of Tropical Medicine in 1941[11]. These symptoms may be conveniently subdivided into 3 categories: constitutional, gastrointestinal and hematologic. Symptoms not directly referred to an organ system were prominent during the course of the illness of these patients. Although 6 had been previously treated with relief of all symptoms of sprue, none had followed the prescribed treatment for a prolonged period of time; they had one or more relapses and never a complete spontaneous remission. Weight loss had been marked and steady during the periods of exacerbation. Other constitutional symptoms volunteered by all of the patients in this group were weakness and lassitude, often amounting to listlessness.

Gastrointestinal symptoms elicited from all of the present group of patients included abdominal discomfort, flatulence and intolerance to rich foods. Atrophy of the lingual papillae with or without redness and soreness was observed in 6 of the 9 patients. A clear-cut history of soreness and redness of the tongue was obtained from 2 of the remaining 3. Histamine achlorhydria was present in 4, hypochlorhydria in 2 and a normal gastric acidity curve in the other 3 patients. Diarrhea had been present in all. At the time of admission, 8 had diarrhea. The amount, frequency and consistency of the depositions varied considerably. In all patients the stools were of light brown or yellow color and of foul, pungent odor. Bulky and greasy stools were noted in only 4 of the patients. The oral glucose tolerance curves were flat. No ova of pathogenic parasites were discovered from single stool specimens examined at the time of admission.

The hematologic data collected differed in no way from those of pernicious anemia. All the patients had a macrocytic anemia of less

* The folinic acid employed in this study was supplied to us by Dr. Woodson C. Young, of Eli Lilly & Co. One unit of this material is equivalent to approximately one microgram of pure citrovorum factor.

than 2.5 million red cells per c.mm., and a megaloblastic bone marrow.

The salient clinical and laboratory observations are recorded in Tables 1 and 2. Other laboratory studies necessary for the evaluation of the response to therapy are noted in the figures corresponding to the individual case reports (Figs. 1 to 9). Reticulocyte counts were performed daily. Complete blood counts were done once a week. Bone marrow smears were done before and after treatment, except in Case No. 5.

None of the patients selected had received hematinics for at least 10 weeks prior to treatment with folinic acid. On admission they were allowed a basic diet containing no meat or eggs and calculated to correspond in caloric and vitamin content to the average diet of low income groups of Puerto Rico. Seven were kept on this diet throughout the entire period of observation. Two required dietary modifications which will be discussed later. By the use of tabulated cards upon which the patients recorded the proportion of their servings ingested at each meal (as 1+, 2+, 3+, or 4+) their appetite and caloric intake were roughly gauged. The body weights were recorded daily.

The 9 cases were divided into 2 groups. The first 5 were treated at the Veterans Administration Hospital where facilities were available for extending hospitalization beyond the period of treatment in order to observe the laboratory and clinical changes that followed. The results of treatment were thereby fully evaluated. With this group of patients we felt our way until we had established a treatment schedule which approximated the minimum total dose that should bring about a maximum therapeutic effect. This schedule

TABLE 1.—CLINICAL AND LABORATORY FINDINGS IN NINE CASES OF SPRUE PRIOR TO TREATMENT WITH FOLINIC ACID

Case No.	*Diarrhea*	*Glossitis*	*Gastric Acidity (after histamine)*	*Oral Glucose Tolerance*	*Weight Loss Over 10 lb. in 3 Months*	*Small Intestine Roentgen Series*
1	+	+	0	Flat	+	Deficiency Pattern
2	+	+	0	Flat	+	Deficiency Pattern
3	+	+	+	Flat	+	Deficiency Pattern
4	+	+	+	Flat	+	Deficiency Pattern
5	+	History of	0	Flat	+	Not Done
6	+	+	+	Flat	+	Not Done
7	History of	History of	+	Flat	+	Not Done
8	+	+	0		+	Not Done
9	+	+	+	Flat	+	Not Done

TABLE 2.—HEMATOLOGIC DATA IN NINE CASES OF SPRUE BEFORE TREATMENT WITH FOLINIC ACID

Case No.	*RBC Millions*	*HGB Gm. per 100 cc.*	*Vol. RBC cc.*	*M.C.V.*[1] *c.μ.*	*M.C.H.*[2] *μ.μ.g.*	*M.C.H.C.*[3] *%*	*W.B.C.*	*Megaloblasts in Bone Marrow*
1	1.64	7.7	25	152	47	31	3,400	15.4
2	1.38	7.6	20	145	55	38	5,500	17.0
3	2.21	8.7	33	150	39	26	9,450	9.4
4	1.78	9.9	31	172	55	32	5,150	39.8
5	0.89	2.8	12	135	31	23	2,550	—
6	1.51	6.4	21	139	42	30	7,150	7.0
7	2.06	7.2	21	102	35	34	3,800	7.5
8	1.90	7.2	22	116	38	33	8,890	10
9	1.90	7.7			38		5,550	10

[1] Mean corpuscular volume.
[2] Mean corpuscular hemoglobin.
[3] Mean corpuscular hemoglobin concentration.

of treatment was to be employed in all the remaining cases. The second group, which consisted of 4 patients, received treatment at the San Juan City Hospital under similarly controlled circumstances. The period of observation in these patients, however, was limited to the period of treatment. The immediate clinical and hematologic response was noted and thereafter the patients were started on a full diet and on parenteral liver extract so that they could be discharged at the earliest possible date. The immediate results of treatment with folinic acid in this group proved of value in corroborating or disproving some of the general conclusions drawn from the more detailed observations on the first group.

previously he had lost 30 pounds in weight. He appeared cachectic and weak. He complained of slight burning of the tongue which was smooth and glossy but of normal pink color. He was having 5 to 6 liquid, pale yellow, malodorous bowel movements daily.

Treatment with folinic acid was started on 9/1/50; 100 units were injected daily for 12 days. On the 6th day of treatment the patient appeared brighter, ate better and his stools became creamy. This slight clinical improvement which corresponded with a slight rise in circulating reticulocytes (Fig. 1), was very transitory. By 9/23 anorexia and diarrhea were again marked, as before treatment. Persistent megaloblastosis was

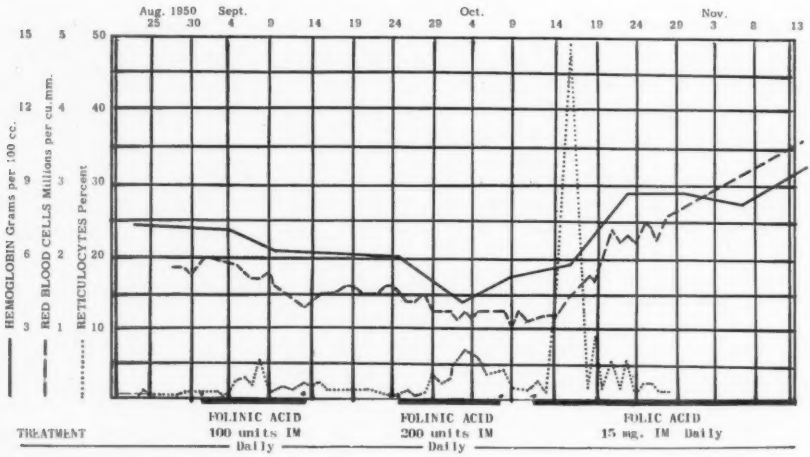

FIG. 1.—CASE 1.

Case Reports. CASE 1. A white farmer aged 53 was admitted to the Veterans Hospital on 8/1/50. The onset of his illness was in 1923 with profuse, watery diarrhea. Within 10 months he had lost 65 pounds in weight and had become extremely weak. He was fed large amounts of liver and experienced slow but steady improvement. In 1933 this treatment was supplanted by parenteral liver extract. In his home environment, however, he was unable to follow the prescribed regimen. Up to 1950 he had been hospitalized 10 times for treatment of recrudescences. The exacerbation of symptoms which led to this hospitalization was of about 1 year's duration and of progressive severity. Since his last liver injection one and one-half years

demonstrated by repetition of the bone marrow aspiration on 9/26. A second course of folinic acid was then started. Two hundred units were injected daily for 12 more days. As previously, the clinical evidences of improvement were minimal. Three days after completion of the second course of folinic acid the diarrhea became very profuse. The patient became so weak and dehydrated that energetic treatment was immediately started: 15 mg. of folic acid were injected intramuscularly each day. The basic no-meat no-eggs diet was not changed. The hematologic response as noted in Fig. 1 was dramatic. Gain in strength, appetite and weight was slow but sustained. By 10/28 the stools were formed and brown, and young papillae had

covered the entire tongue. The patient was discharged 12/1/51, at which time his RBC count was 3.7 millions and his hemoglobin 10 gm.

The secondary reticulocytosis following the use of folic acid proved that this patient was susceptible to average therapeutic doses of a well known hematinic. Inasmuch as there is a close relationship between folinic acid and folic acid, it was reasonable to assume that the failure of folinic acid to elicit a satisfactory response was ascribable to inadequacy of the dosage of folinic acid employed.

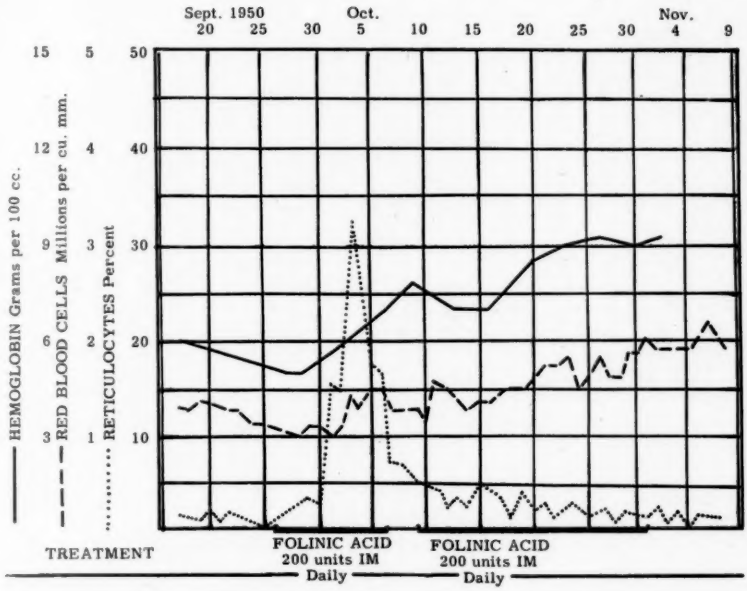

FIG. 2.—CASE 2.

CASE 2. A 57-year old mulatto entered the Veterans Hospital on 9/5/50, complaining of severe weakness and diarrhea. For an undetermined period of time prior to 1947 he had watery diarrhea and progressive weakness. In 1947 he was hospitalized at another hospital where a diagnosis of sprue was established. He improved considerably after receiving folic acid by mouth and injections of liver extract. He did not continue treatment following discharge from the hospital. During the 4 months that preceded this hospitalization, he felt progressive weakness, loss of weight, diarrhea (4 to 7 times daily) and burning of the tongue. On physical examination he appeared wasted and very weak. The tongue was smooth and bright red. The skin was dry and inelastic. The feces were creamy or liquid, contained many undigested food particles and had a penetrating fetid odor.

On 9/26/50 treatment with folinic acid was started. Two hundred units were injected daily for 12 days. By the 6th day of treatment improvement in appetite was in evidence. On the following day the feces became mushy and homogeneous. Coincidentally with this definite clinical improvement, the peak in reticulocyte response was reached (Fig. 2). This was the first case in which we were able to observe an encouraging clinical and laboratory response. It was therefore decided to continue treatment and to observe carefully the clinical course. The basic diet was not altered. Two hundred micrograms of folinic acid were given daily for 25 more days. Young lingual papillae were first noted on 10/18/50.

Throughout the entire period of treatment, the weight gain was steady, and a definite improvement in the hematologic picture was noted. The leukocytes rose from pre-treatment leukopenic levels to high normal levels after the second week of treatment. The red blood cell count, however, did not rise sharply. On 11/6/50, a bone marrow smear revealed persistent megaloblastosis (5.7%) and erythroblastic arrest. There was a rise in circulating eosinophils to 28% after 25 days of treatment. No allergic manifestations were observed at any time. After discontinuation of folinic acid the eosinophil count gradually fell, but rose again following the administration of oral folic acid after 11/6/50. The patient left the hospital on 11/27/50.

The response in this case was very encouraging but puzzling at this stage. Inasmuch as the minimal effective dose of a given therapeutic agent varies from one patient to the next, we were at the crossroads in trying to decide whether the first patient was unusually refractory or the second patient unusually susceptible to treatment with folinic acid. The latter seemed more probable in view of the meager erythrocytic response in the second case and the persistence of megaloblasts in the bone marrow at the end of treatment. We decided therefore to double the amount of folinic acid to be administered to the next case.

Case 3. A 63-year old white male was admitted to the Veterans Hospital on 1/10/51, complaining of recurrent bouts of diarrhea, weight loss, weakness and pallor for 7 years. He had been hospitalized many times for these symptoms, but had been unable to procure the prescribed medications after leaving the hospital. In February, 1950, he received liver injections for the last time prior to this admission. When he entered the hospital he complained of vague abdominal discomfort and of soreness of his tongue. Although able to move about, he preferred to stay in bed and exhibited no interest in his environment. Physically he appeared much older than his stated age. Acne rosacea of his cheeks concealed his pallor. His tongue was devoid of papillae except for a

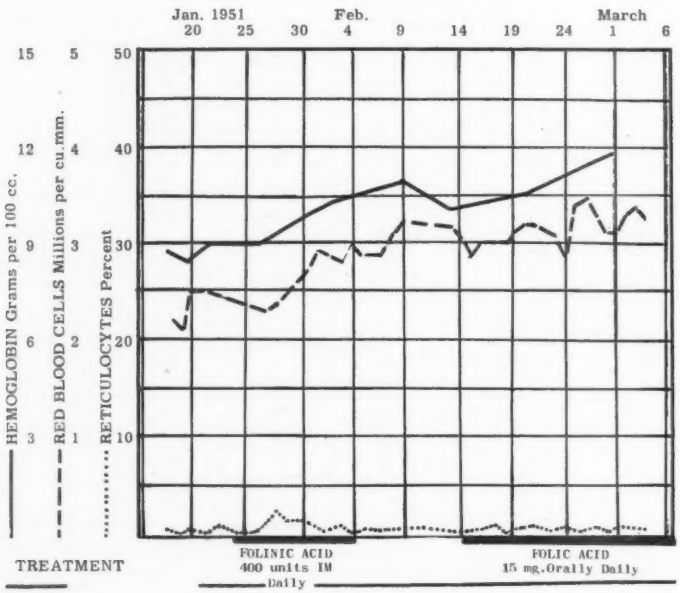

Fig. 3.—Case 3.

small patch in the middle. He was having 6 to 10 liquid, yellowish brown and very fetid bowel movements daily. Unfortunately, for some undetermined reason there was a spontaneous remission of the diarrhea prior to treatment.

Folinic acid was administered in 400 units daily for 12 days, between 1/24 and 2/5/51. A slight reticulocytosis of 2.9% was obtained on the 4th day of treatment (Fig. 3). Some clinical improvement manifested by gain in appetite and strength was noted on the 6th day of treatment. A bone marrow smear obtained at the end of therapy disclosed persistence of megaloblasts. The patient continued to improve clinically. Three weeks after the first injection of folinic acid he was ambulatory most of the day and partook with interest in the recreational activities of the hospital. There was a rise in circulating erythrocytes (Fig. 3) from an average of 2.4 millions per c.mm. before treatment to 3.2 millions, 16 days later. The subsequent injection of 15 units of folic acid daily produced no secondary rise in reticulocytes. The red cell count continued to climb and clinical improvement prevailed until discharge 3/14/51.

The failure to obtain a significant reticulogenic response in this patient cannot be accounted for with any degree of certainty. The dosage of folinic acid employed may have been sufficient to produce a remission of all symptoms and an erythrogenic response but insufficient to elicit a reticulocytosis. This inference would presuppose a peculiarity of action of folinic acid such as had been pointed out by other workers[6]. At the time we were treating this patient we read the reports of Spies and co-workers[14] in which they described satisfactory reticulogenic responses to citrovorum factor administered in very high doses. We decided therefore to step up the dosage once again for the treatment of subsequent patients.

CASE 4. A 33-year old white male was admitted to the Veterans Administration Hospital on 1/29/51. In 1944 while in the Service he developed peptic ulcer symptoms. Two months later, while partaking well of the average Army diet, he had onset of diarrhea, with 4 to 5 bulky, foamy, yellow stools daily. Soon thereafter he sought medical advice for the recurrent epigastric pain. A Sippy diet was prescribed which resulted in relief of his pain. The diarrhea was partially controlled by anti-acid medicaments. After separation from the service he adhered to this regimen very haphazardly. The diarrhea continued intermittently. By January, 1950, he had lost considerable weight and had become very weak. He was then given parenteral liver extract for the first time and had a short period of complete remission. He did not follow instructions and had a recurrence of all symptoms, including the ulcer pain. Notwithstanding the short period of improvement early in 1950, he had lost, by January, 1951, 65 pounds in weight. On physical examination he appeared wasted, weakened, listless, and quite pale. The tongue was smooth at the tip but not otherwise remarkable. The feces were creamy in consistency, frothy, abundant and light yellow. Instead of the basic diet this patient was given cooked cereals and starchy vegetables 3 times a day and hourly feedings of 3 ounces of milk enriched with milk powder and dextrose. The caloric allowance of this diet was considerably more than that of the basic diet. Due to marked anorexia, this patient did not eat more than half of his servings at each meal until the effects of folinic acid became apparent.

Treatment with 1,000 units daily of folinic acid was started on 2/7/51, and continued for 12 days. Clinical improvement was noticed on 2/11/51. His listlessness rapidly disappeared and he became one of the most helpful patients about the ward, before the completion of the course of folinic acid. In 2 weeks he gained 10 pounds in weight, despite the fact that the diarrhea persisted until the hourly milk regimen was discontinued on 2/23/51. A second bone marrow obtained on February 19, 1951, showed marked evidence of erythroblastic activity. The percentage of megaloblasts had dropped from 39.3 to 9.2. After the circulating reticulocytes had fallen to pre-treatment levels, a sprue diet modified by the exclusion of meat and foods containing coarse fibers was allowed and daily folic acid was given by mouth. There was no significant secondary reticulocytosis (Fig. 4). At the time of discharge, 3/26/51, the erythrocytes count was 4.0 millions per c.mm. and the hemoglobin 13.3 gm.

This patient showed a very satisfactory clinical remission, and rise in cir-

culating erythrocytes, despite a meager reticulocytosis. It is noteworthy that the diarrhea did not cease until the enriched milk was discontinued. Many peptic ulcer patients develop diarrhea when they are given hourly feedings of enriched milk. In this patient the restoration of normal bowel function after withdrawal of the excess carbohydrate is indicative of definite improvement in the absorptive function of the intestine as a result of treatment with folinic acid.

was given 6 units of crude liver extract intramuscularly every day and his improvement was unsatisfactory. He had a meager reticulogenic response of 5.7% and a very slow rise in circulating erythrocytes. He received hematinics for the last time prior to this admission in November, 1950. Exacerbation of symptoms was apparent in January, 1951. In 3 months he lost 20 pounds in weight and experienced such weakness that he was hardly able to move about. On physical examination he appeared pale, wasted and very weak. The tongue was normal except for pallor. There was a mottled discoloration of his palms and soles which had been noticed in the last two months. A bone mar-

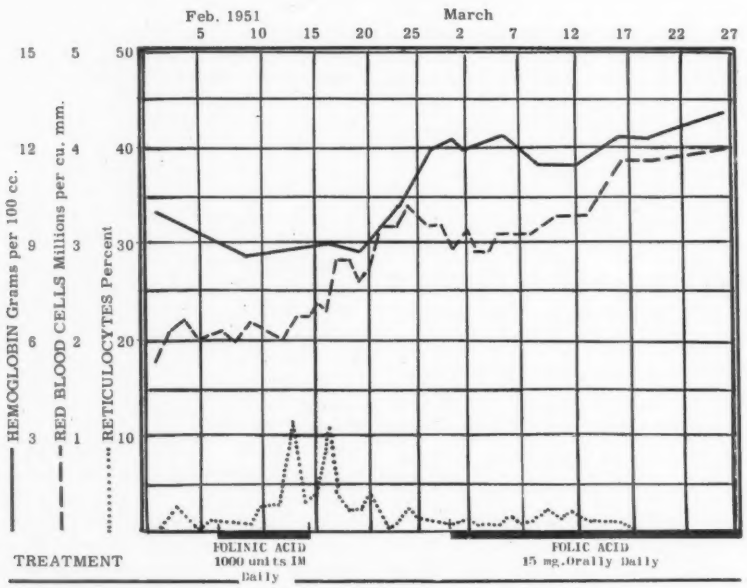
Feb. 1951
March
5 10 15 20 25 2 7 12 17 22 27
HEMOGLOBIN Grams per 100 cc.
RED BLOOD CELLS Millions per cu. mm.
RETICULOCYTES Percent
15 12 9 6 3
5 4 3 2 1
50 40 30 20 10
TREATMENT
FOLINIC ACID 1000 units IM Daily
FOLIC ACID 15 mg. Orally Daily

FIG. 4.—CASE 4.

CASE 5. A 41-year old white farm laborer was admitted to the Veterans Hospital on 4/4/51. He volunteered a history of recurrent diarrhea, frequent soreness of the tongue, weakness and pallor since August, 1949. Since the onset of his illness he had been hospitalized 3 times and had been treated with parenteral liver extract, Vitamin B_{12} or folic acid alone or in various combinations. It is of interest that in August and September, 1949, this patient had received Vitamin B_{12} by mouth at this institution and showed no significant clinical or hematologic evidence of improvement. Subsequently he

row smear could not be secured on current admission. Smears obtained in this hospital during previous hospitalizations had repeatedly revealed megaloblastosis up to 24% before treatment.

During the first 4 days of observation the patient entered a critical phase of his illness. He gained 10 pounds in weight. Edema of the dependent parts became apparent. He developed extreme weakness and listlessness. Treatment was therefore instituted without delay on 4/9/51, with 1000 units of folinic acid injected daily for 12 days. On the second day of treatment he felt

somewhat brighter and ate better. The feces became formed after the 4th day of treatment. By the 7th day of folinic acid and concomitantly with the peak in reticulocyte response (Fig 5), he had a 6-pound diuresis. From there on he had a sustained clinical improvement with gradual disappearance of all symptoms. The pigmentation of the hands, however, did not disappear. There was no reticulocytosis following the oral administration of folic acid 5 mg. 3 times a day. This treatment was started on 5/3/51, and continued until the time of discharge 5/23/51, when he was prescribed a maintenance dose of folic acid.

swelling of his ankles. Up to the time of admission he had lost about 16 pounds in weight. Weakness was rapidly progressive so that at the time of examination he was unable to walk over 50 feet without having to rest. There were moderate papillary atrophy of the tongue and redness of its tip. There was a blowing, grade 1 systolic murmur at the cardiac apex.

Folinic acid therapy was started on 2/18/51. On the 4th day of treatment sternal marrow megaloblasts had decreased to 2.5%. On the 5th day considerable clinical improvement was in evidence. He felt progressively stronger and began to increase

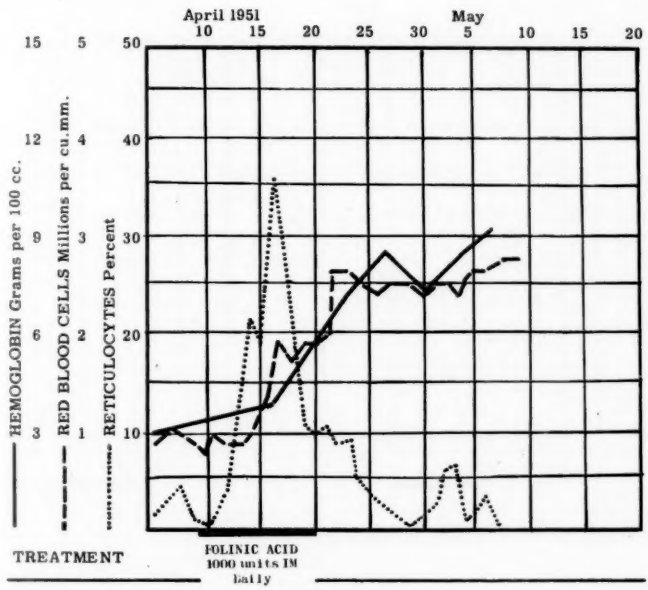

FIG. 5.—CASE 5.

The response to treatment with folinic acid was satisfactory in every respect. The fact that it proved very effective in a case in which crude liver extract had failed to induce a satisfactory remission is of added significance.

CASE 6. A white man, aged 56, was admitted to the San Juan City Hospital on 2/9/51. Two months before admission he noticed that his stools became soft and pasty and increased in number. Concomitantly he became aware of easy fatigability and slight

his activity about the ward. He developed a voracious appetite. By the 6th day the burning of the tongue had disappeared and the redness started to subside. The feces became formed and darker in color. On 3/2/51 no megaloblasts were found in the sternal marrow smear. On 3/4/51, two days after the substitution of liver extract for folinic acid, he was discharged from the hospital.

Effective control of all the symptoms of sprue was rapidly attained in this case. The sharp rise in circulating

reticulocytes and in the red blood count is illustrated in Fig. 6.

CASE 7. A 65-year old white foreman was admitted to the San Juan City Hospital on 2/23/51. Ten years previously he had developed severe diarrhea, redness and soreness of the tongue and progressive weakness. Two months later he was hospitalized after having lost about 15 pounds in weight. After receiving a series of injections of liver extract he improved dramatically. He continued to receive short courses of liver extract injections every 3 to 6 months up to about 1948. In December, 1950, he developed generalized abdominal discomfort after meals, progressive weakness and pallor. By the time of admission he had lost 10 pounds in weight. He tired easily on walking and experienced frequent dizziness. The tongue was pale but exhibited no papillary atrophy.

One thousand units of folinic acid were injected daily for 12 days, between 3/4/51 and 3/15/51. Definite improvement in vigor and appetite was apparent by 3/10/51. All abdominal symptoms subsided before the completion of treatment with folinic acid. A sternal marrow smear performed at the end of folinic acid therapy revealed virtual disappearance of megaloblasts (0.5%). After a distinct rise in red cell count was in evidence, treatment with liver extract was started in preparation for discharge on 3/24/51.

In the absence of diarrhea and glossitis during the current exacerbation of this patient's illness, we had very few objective signs by which to evaluate the clinical improvement of this patient. He volunteered unhesitatingly, however, that the marked abdominal discomfort and loss of energy which he had experienced, disappeared rapidly. The reticulocytosis and erythrogenic response illustrated in Fig. 6 are comparable to those observed in the previous case.

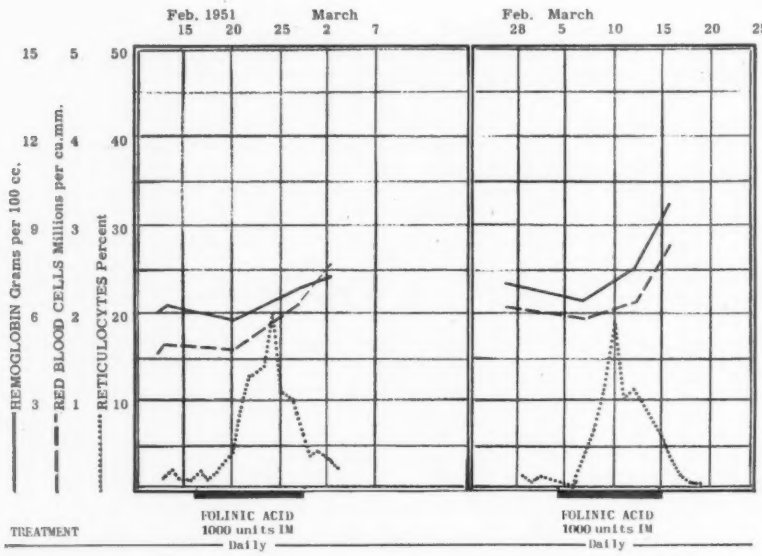

FIG. 6.—CASE 6. CASE 7.

CASE 8. A 19-year old mulatto was admitted to the San Juan City Hospital on 3/19/51. Three months previously he developed progressive weakness, anorexia, weight loss and burning of his tongue, oral mucosa and throat. Diarrhea appeared 3 weeks before admission and consisted of 4 or 5 large, fetid, frothy, yellowish-green,

watery bowel movements per day. In the 2 weeks that preceded admission he was bedridden because of extreme weakness. He appeared cachectic and very pale. The corners of his mouth were fissured; the gums were spongy and bled easily. The tongue was red and exhibited marked atrophy of the papillae. The patient had a low-grade irregular fever.

One thousand units of folinic acid were injected daily for 12 days. Treatment was started the day after admission to the hospital, in view of the critical state of debility of the patient. In addition a high protein intake was allowed, but no meat or eggs were included in his diet. Bismuth and paregoric were given orally in order to prevent further debilitation due to profuse diarrhea. On the 5th day of treatment the burning of the oral mucous membranes and tongue disappeared. On the 6th day the appetite was definitely better and the stools, which had remained liquid despite the use of an antidiarrheal mixture, became mushy and medium-sized and lost their characteristic foul, penetrating odor. During the first hospital week the patient gained 8 pounds in weight. On the 9th hospital day, however, symptoms and signs of obstruction of the small intestine developed. Small bowel dilatation and multiple fluid levels were demonstrable radiographically. In view of the previous debilitating illness which led rather rapidly to this complication, tuberculous enteritis and peritonitis were strongly considered despite a perfectly clear lung roentgenogram. The spinal fluid was clear, with no increase in cells or rise in protein content. Penicillin, streptomycin, Vitamin C and B, parenteral fluids and two 500-cc. blood transfusions were given. The patient became unresponsive though never comatose. He improved gradually of his physical condition but remained mentally dull. He was withdrawn from his environment and unable to care for himself. Once during convalescence he had a grand mal seizure. Tuberculosis was never proven. He was discharged from the hospital on 5/16/51. One of us (C. A. R.) visited him at home one month later and found him well nourished and active but irrational, uncooperative and withdrawn. He was eating voraciously and had no diarrhea, glossitis or cheilosis.

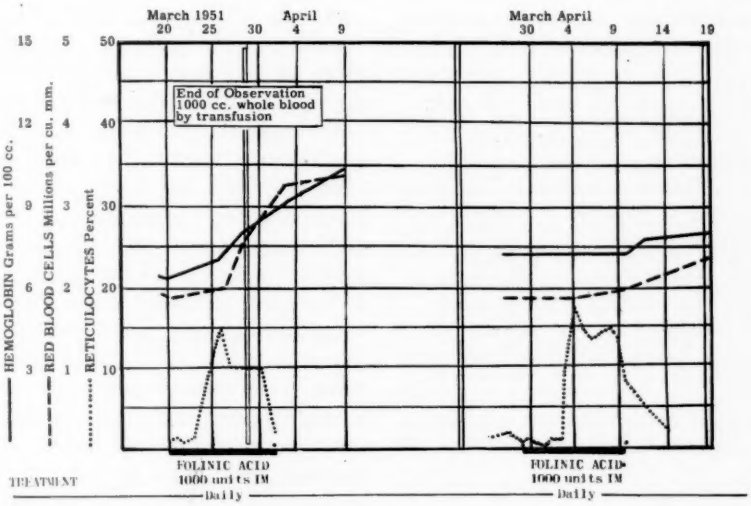

FIG. 7.—CASE 8. CASE 9.

This patient unquestionably fulfilled the necessary clinical and laboratory criteria for the diagnosis of sprue. The course of events suggested, however, that some other intestinal disorder could be responsible for the syndrome. Although no other disease entity could be incriminated, we prefer to classify this patient's condition separately as

one of sprue syndrome of undetermined cause. He received folinic acid for 12 days, but the protocol observation had to be abruptly ended on the 9th day of treatment. The blood changes prior to that date (Fig. 7) illustrate the hematologic improvement. Two marrow smears, done on the 11th and 13th day after the start of folinic acid treatment and before the administration of liver extract, revealed disappearance of megaloblasts. We have no reason to believe that the complicating intestinal obstruction or the mental changes were related in any way to the administration of folinic acid.

CASE 9. A white woman, aged 29, was admitted to the San Juan City Hospital on March 26, 1951. Six months previously she had onset of diarrhea, anorexia, abdominal discomfort and intermittent burning of the tongue. Ten weeks before admission she received 5 liver injections of unknown concentration, with no distinct improvement. By the time of admission she had lost 31 pounds in weight. She was having 6 to 8 yellow, bulky, frothy and fetid bowel movements daily. The skin and mucous membranes were pale. There was redness and moderate papillary atrophy of the tongue. The abdomen was somewhat protuberant and tympanitic.

Folinic acid was injected for 12 days in single daily doses of 1000 units. After the 3rd day of treatment she began to feel stronger. By the 6th day she was having 2 formed, brown movements daily. Despite the deficient diet on which she was maintained during the period of observation, she gained 7 pounds in weight in 2 weeks. A bone marrow smear at this time disclosed a fall of megaloblasts to 2%. Daily parenteral liver extract was substituted for folinic acid on 4/10/51, and continued until the date of discharge 4/22/51.

The clinical improvement in this case was dramatic. The reticulocytic response was satisfactory. Unfortunately, treatment with liver extract was instituted before demonstrating a rise in the concentration of circulating erythrocytes (Fig. 7). We have no proof that the significant increment in the red blood count which was subsequently observed, was due to the hematinic effect of folinic acid or of liver extract or a combination of both agents. We have therefore classified this case as one that exhibited a submaximal erythrogenic response to the dosage schedule of folinic acid employed.

Discussion. No local or generalized untoward effects were observed in 9 patients treated with folinic acid administered by deep intramuscular injection. One patient exhibited a marked eosinophilic reaction unassociated with signs or symptoms of drug sensitivity. We believe that this represents an eosinophilic response to the hematinic, such as has been observed as a response to liver and folic acid therapy in cases of pernicious anemia as well as sprue.

The reticulogenic response to citrovorum factor or folinic acid has received the attention of all the clinical investigators who have employed this agent to date. Ellison and co-workers[6] noted lack of correlation between the erythrogenic and reticulogenic responses in pernicious anemia patients treated with 5 to 10 million units of citrovorum factor daily. Although we have noted a similar disparity in at least one of our cases (Case 4), we are unable to reach any conclusions in this regard. It should be pointed out that the standards for maximum reticulocyte response which have been calculated for cases of pernicious anemia[9] are not necessarily applicable to sprue. As a matter of fact, it is our clinical impression that the reticulocytic responses to effective sprue therapy are, on the average, lower than those obtained in pernicious anemia. Among the 50 cases of sprue treated with folic acid by Suárez and co-workers[16], for instance, there were several who received large daily doses of folic acid

and whose reticulocytic responses were well below the "average" expectancy, if judged by the standards set up by Isaacs and Friedman[8] for pernicious anemia treated with parenteral liver extract. By all other criteria these same patients had excellent clinical and hematologic responses. Nevertheless, 5 of our 6 cases treated with 1000 units of folinic acid daily reached peaks of reticulocyte percentages which approximated closely the average expectancy of reticulocyte peaks in patients with pernicious anemia treated with parenteral liver extract and having similar erythrocyte counts.

The erythrogenic response to treatment with 1000 units of folinic acid daily was satisfactory in 5 of 6 cases, when measured by the standards of Isaacs, Bethell, Riddle and Friedman[7] for pernicious anemia patients treated with intramuscular liver extract. The poor erythrogenic response observed in Case 9 was surprising in view of the reticulocytosis and the excellent clinical improvement observed.

All of the 6 patients who received 1000 units of folinic acid daily for 12 days exhibited marked improvement of all of the clinical symptoms of sprue which had been noted at the time of admission. The successful and swift control of the diarrhea and other gastrointestinal symptoms by this new agent is of interest, inasmuch as this effect is not marked when Vitamin B_{12} is employed in the treatment of sprue, but it is striking whenever folic acid is used. This observation, in view of the established relationship of folic acid and folinic acid, would suggest that the latter substance retains the specific properties of folic acid which correct or compensate for the absorption deficiencies in sprue.

The clinical and hematologic improvement obtained in 6 cases of sprue in which 1000 units of folinic acid were administered daily is similar to the improvement obtained following treatment with 10 to 15 mg. of folic acid daily[16]. Inasmuch as 1000 units of folinic acid are equivalent to approximately 1000 micrograms of pure citrovorum factor, it appears that weight by weight, folinic acid is 10 to 15 times more effective than folic acid in the treatment of sprue.

The exact role of folinic acid in the biochemical processes that have to do with the maintenance of the integrity of intestinal absorption and blood formation, remains to be determined. Since folic acid has been the most effective single therapeutic agent which we have employed in the treatment of sprue we should like to speculate further on the functional relationship of these 2 substances. Schoenbach *et al.*[13] demonstrated that citrovorum factor could correct the toxic manifestations of therapy with folic acid antagonists. The inability of folic acid to bring about the reversal of these toxic manifestations may signify that the so-called folic acid antagonists block the conversion of folic acid into a metabolically more active substance, similar to or identical with citrovorum factor. In the light of these observations the results obtained in our series suggest that folinic acid may be more closely related to the basic deficiency or deficiencies responsible for the development of sprue than to other active substances which have been studied heretofore.

Summary. 1. Three cases of sprue were treated with 100 to 400 units of folinic acid intramuscularly for 12 days. All exhibited hematologic and clinical improvement which we consider inadequate.

2. Six other cases of sprue received 1000 daily units of folinic acid by intramuscular injection for 12 days. a) The clinical symptoms of the dis-

ease were rapidly and effectively controlled in all. b) The hematologic improvement was adequate in 5 and submaximal in 1.

3. There were no untoward effects from the administration of this agent by the deep intramuscular route.

4. We believe that folinic acid is qualitatively as effective as folic acid in the treatment of sprue. Weight by weight this substance appears to be 10 to 15 times more active than folic acid in the treatment of sprue and may well represent a derivative of the latter agent which retains all of its anti-sprue activity.

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SEDIMENTATION RATE IN MYOCARDIAL INFARCTION

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The sedimentation rate in coronary occlusion and myocardial infarction is a most useful diagnostic procedure. The present investigation was undertaken to confirm the accuracy of this method and to attempt an evaluation of its usefulness as a guide in the management of the patient, especially with regard to such matters as getting the patient out of bed and exercise.

The value of the sedimentation rate in coronary disease was first shown conclusively by Rabinowitz, Shookhoff and Douglas[5]. Since that time several good studies of the behavior of the blood sedimentation have appeared but some questions have remained unanswered. How long does the sedimentation rate remain elevated in uncomplicated cases? Does a persistently elevated rate call for prolonged bed rest in a patient otherwise well?

The present study comprises 100 consecutive cases of major myocardial infarction, the diagnosis having been confirmed in all cases by definite electrocardiographic changes or postmortem examination. The cases were seen at the Kings County Hospital, University Division, the Bushwick Hospital, the Long Island College Hospital and in private practice. Several methods of determination were used. In most cases the Wintrobe method was employed with correction by hematocrit determination. The cases chosen were of major myocardial infarction, presumably the result of occlusion of a main coronary artery in most cases. As usual in the evaluation of statistical data concerning myocardial infarction, we encountered the difficulty of determining accurately the exact time of infarction. In some cases it is possible to do this with some accuracy but in many, if not most instances, it is impossible because of premonitory pain or the mildness of symptoms. This is a problem beyond the scope of this paper except that a consideration of this sort affects the statistical analysis of this and other studies of myocardial infarction. Cases of coronary insufficiency or subendothelial infarction will be considered elsewhere.

The sedimentation rate is elevated in almost all cases of major infarction. Shillito[6] found it increased in 98% of his cases. Chambers[2] found it elevated in all of the cases in his series that died and in 90% of his non-fatal cases. In our series the sedimentation rate was more rapid than normal in all cases but 3 (97%). These 3 were all cases which survived.

The time of onset of any increase in the sedimentation rate is still not accurately known. However, it is the last commonly employed sign of myocardial infarction to appear and the longest to persist. Shillito[6] found that there was a slight increase by the 3rd day and a maximum increase from the 4th to the 8th day. Koenig and Young[3] said that it was "probable that acceleration of sedimentation begins in the 1st hour after the thrombotic lesion occurs." Rabinowitz *et al.*[5] stated that the

rate became rapid starting with the 2nd day. Baer and Frankel[1] found the fastest rates on the 2nd to 5th day. In our cases in which the major episode could be timed within an hour or 2, all sedimentation rates taken within 24 hours were normal. Of 22 rates taken between 24 and 48 hours, 13 were high. In 43 cases in which the rate was determined between 48 and 72 hours after the first symptoms, an increase was noted in 40. Therefore it seems reasonable to conclude that a sedimentation rate taken within the first 24 hours will be of little value for comparison with later determinations. A rapid rate found between 24 and 48 hours is of great diagnostic import, a negative one of little value. Between 48 and 72 hours nearly every rate which is going to become rapid, will do so. In a few instances the rate did not become rapid for 4 to 7 days after the onset of an attack. In such patients the sedimentation rate roughly paralleled the late appearance of fever and leukocytosis. In all such cases it was impossible to determine the time of infarction with accuracy and it seems quite probable that the patient was first seen with prodromal pain and that the infarction did not take place until a later time.

In our cases the sedimentation rate was considered rapid if the corrected rate was 18 mm. per hour or over. The range was between 18 and 56. Shillito[6] found the range of highest sedimentation rate to be between 21 and 137. There was no correlation in our cases between the height of the sedimentation rate and severity of the illness or the ultimate prognosis. The maximum rate occurred between the 3rd and 7th day, and in all cases, except those with secondary thromboses, it had started to decline by the 8th day.

The length of time which it takes the sedimentation rate to return to normal has been a matter of considerable concern to the clinician. According to 1 study[6] the sedimentation rate gradually falls to normal by the 28th day. Another observer found it to return to normal between the 13th and the 39th day. In our cases the majority of rates had returned to normal by the 21st day, but there were some which, in spite of the absence of secondary cardiovascular complications, failed to return to normal until the 40th day or later.

As previously stated the *degree of increase* in sedimentation rate had no relationship to the severity of the illness, but it was found that the degree of persistence of the rapid rate correlated definitely with the clinical severity of symptoms. Therefore it was felt that a persistently elevated rate would be an indication for continued bed rest contrary to our usual practice of permitting the patient out of bed on the 22nd day.

Nevertheless there were a goodly number of patients in whom the sedimentation rate remained somewhat elevated despite the fact that they appeared clinically well—at least with respect to the heart. There were 18 such patients in all, in 13 of whom the increase in the sedimentation rate could be explained by extra-cardiac disease; in 5 there was no evident explanation.

In 5 instances the rate remained rapid beyond the 35th day, gradually returning to normal thereafter. In these 5, there was no evidence of extension of the myocardial process, vascular complications or conditions elsewhere in the body which might cause an acceleration of the rate. We have therefore made it a recent practice to keep these patients in bed for a somewhat longer period of time, but in the absence of evidence of cardiac complications, to permit such patients some

degree of ambulation by the 42nd day. In no instance have relapses followed this procedure. We are unable to explain the continued high rate satisfactorily.

There were 3 cases of repeated myocardial infarction during the patients' hospital stay. In each instance, the rate was subsiding toward normal and shortly after the fresh infarction, the rate increased sharply.

We were especially impressed with the number of patients with persistently elevated sedimentation rates as the result of conditions outside the heart. It would be desirable, of course, to have a control rate in all cases but it is only in the rarest instance that we know the level of the patients sedimentation rate prior to the myocardial infarction. It has been necessary, therefore, to assume that all persistently rapid rates are the result of cardiac disease unless conclusively shown otherwise.

In 3 cases a persistently elevated sedimentation rate was found to be the result of an unsuspected malignancy. Two of these were malignancies of the lung and 1 a carcinoma of the pancreas. In 2 cases the elevation was the result of pulmonary tuberculosis and in 4 it was the result of chronic sinusitis and bronchiectasis. In 1 it was the result of rheumatoid arthritis.

There were 3 cases of phlebothrombosis of the veins of the lower extremities. Two of these resulted in pulmonary embolism, 1 ending fatally. In each of these, the sedimentation rate was accelerated without obvious cardiac cause. This complication, of course, has been seen much less frequently since the almost routine use of the anticoagulants in the treatment of myocardial infarction.

According to Meyers[4], an increase in plasma fibrinogen roughly parallels the sedimentation rate. Plasma fibrinogen increases promptly after myocardial infarction and remains elevated until healing. Like the sedimentation rate it is not affected by Dicumarol therapy.

There were 3 cases in which the sedimentation rate remained normal despite massive infarction. In each of these cases, there was no obvious cause for this phenomenon but there was cardiac failure in all.

It can be seen therefore that the sedimentation rate is a highly useful diagnostic aid in major myocardial infarction. It has its greatest value in those cases in which the temperature is not elevated. It may be normal for 48 hours after infarction, at least as far as we can tell by present methods. It is somewhat less useful in evaluating the clinical course of the case. Factors outside the heart may cause a persistently elevated rate and there is a small percentage of cases in which an elevation of the sedimentation rate persists after the patient is clinically well.

Conclusions. 1. The sedimentation rate was elevated in 97 of 100 proved cases of major myocardial infarction.

2. The sedimentation rate is a highly useful diagnostic aid especially when the temperature is elevated little if at all.

3. The rate is seldom elevated before 48 hours after infarction but is increased in almost all cases after 72 hours. The elevation persists for 4 to 8 days and in most cases the rate is back to normal by the 36th day.

4. The rate had returned to normal on the 36th day in 76 of 97 cases. In the remaining 21, 3 had fresh infarction, 13 had disease outside the heart, and in 5 there was no evident explanation for persistence of the rapid rate.

5. If the rate is elevated after the

36th day, extra-cardiac causes should be searched for. In some cases the rate is persistently elevated after the patient is clinically well. In such instances, the patient may be permitted out of bed cautiously by the 42nd day.

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THE EFFECT OF QUANTITATIVE VARIATIONS OF ANTICOAGULANT SOLUTIONS UPON PROTHROMBIN TIME

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In a previous study the authors[4] demonstrated that in hypoprothrombinemia a lesser concentration of anticoagulant solution—such as sodium oxalate or sodium citrate—is required to maintain fluidity of the blood than in euprothrombinemia. These findings suggest that the suspension of blood from dicoumarinized patients in the same amount of anticoagulant solution as that from normal individuals, namely, 1 volume of 0.1 molar solution of sodium citrate or sodium oxalate to 9 volumes of blood, leads to a relative excess of anticoagulant solution.

In the determination of prothrombin time, calcium interacts with the anticoagulant—sodium oxalate or sodium citrate—at the moment of addition of calcium chloride, aside from its effect upon the coagulation mechanism proper. A relative excess of anticoagulant solution would, therefore, have to exert an influence upon the required concentration of calcium. In 1938 Stewart and Pohle[8] reported the effect of varying concentrations of calcium upon the prothrombin time in normal individuals and in patients with obstructive jaundice. They found that an excess of calcium as well as an insufficient amount of calcium prolonged the prothrombin time, particularly in the cases of obstructive jaundice.

In 1945, Jaques and Dunlop[1] demonstrated that the concentration of calcium considerably influences the prothrombin time of plasma from dicoumarinized dogs. They reported that normal dog plasma gave little variation in prothrombin time with calcium concentrations varying from 0.005 to 0.1 molar solution of calcium chloride, but plasma from dicoumarinized dogs showed a definite optimal calcium concentration of 0.025 molar solution. They also demonstrated that stronger and weaker concentrations gave much longer prothrombin times. These findings were subsequently confirmed by Quick[6]. In a later study Jaques and Dunlop[2] demonstrated that dog plasma treated with aluminum hydroxide showed the same "sensitivity to the concentration of calcium" as they observed with dicoumarinized plasma.

The above suggested hypothesis of a relative excess of anticoagulant solution in dicoumarinized plasma seems to offer a logical explanation of this phenomenon. It also demonstrates the quantitative relationship between anticoagulant solution and calcium concentration. It was assumed, therefore, that the presence of a relative excess of anticoagulant solution in dicoumarinized plasma may be partly re-

sponsible for the "sensitivity to the concentration of calcium."

In order to substantiate this hypothesis, 2 groups of experiments were carried out. First, it was attempted to produce the sensitivity to the changing concentration of calcium chloride in normal plasma by increasing the concentration of the anticoagulant solution, and second, it was sought to abolish this sensitivity to the changing concentration of calcium chloride in hypoprothrombinemic plasma by decreasing the amount of the anticoagulant solution.

Experimental. A. Effect of Concentration of Anticoagulant Solution Upon Prothrombin Time of Normal Plasma. 1. *Absolute increase of concentration of anticoagulant solution.*

The effect upon the prothrombin time of an excess amount of anticoagulant solution such as sodium oxalate or sodium citrate added to normal human blood was studied in two series of experiments. In the first group of determinations, the concentration of sodium citrate was increased from 0.1 molar to 0.2 molar solution. The prothrombin times were studied with calcium concentrations ranging from 0.01 to 0.16 molar solution (Table 1). Utilizing the photoelectric modification of the one-stage Quick method[3], it was found that with the higher concentration of sodium citrate the prothrombin time obtained with 0.01 molar solution of calcium chloride was excessively prolonged to 211.5 seconds (Table 1). Furthermore, it was noted that the optimal prothrombin time was obtained with 0.02 molar solution of calcium chloride in the plasma containing the usual concentration of sodium citrate. However, the plasma derived from blood added to 0.2 molar concentration of sodium citrate yielded an optimal prothrombin time with 0.04 molar concentration of calcium chloride. This indicates that a higher concentration of anticoagulant solution requires a corresponding increase of the concentration of calcium chloride. In addition there also was a prolongation of the optimal prothrombin time to 16.5 seconds, as compared with 13.2 seconds in the conventional determination. Identical experiments were carried out with normal oxalated plasma utilizing the naked eye method of Quick[5]. The results were similar to those obtained with citrated plasma (Table 2).

2. *Relative increase of concentration of anticoagulant solution by reduction of the amount of added blood.* Attempts to demonstrate the above phenomena with oxalated plasma were not successful with the photoelectric method of determination of the prothrombin time because of the heavy precipitate of calcium oxalate formed in the specimens of plasma obtained with the 0.2 molar concentration of sodium oxalate. In view of this technical difficulty the relative concentration of anticoagulant solution was subjected to variation by changing the quantity of blood added to the standard amount of 0.5 cc. of 0.1 molar solution of sodium oxalate. Three such tubes were prepared and a total of 13.5 cc. of normal venous blood were distributed as follows: 2.5 cc., 4.5 cc. and 6.5 cc. were added to the first, second and third tube, respectively. Whereas the prothrombin time in the previously described experiments was markedly prolonged at 0.01 molar concentration of calcium chloride, a similar prolongation was obtained in this group of experiments when the calcium-chloride concentration was reduced to 0.00125 molar solution (Fig. 1). It was noted that at this concentration the prothrombin time was highest in plasma specimens containing the relatively highest concen-

tration of anticoagulant solution and lowest in plasma samples containing the lowest concentration of anticoagulant solution. Similarly, the shortest prothrombin time, 11.9 seconds, of the entire group of determinations was obtained with plasma containing the smallest concentration of anticoagulant solution and a correspondingly low molar concentration of calcium chloride, namely, 0.005.

and 0.025 molar concentration. While normal blood remained fluid in the tubes containing the 0.1 molar concentration and clotted in the tube containing 0.025 molar concentration of sodium oxalate, this latter tube remained fluid whenever hypoprothrombinemic blood was used. This is in conformity with our previous experience[4], and became evident whenever the prothrombin time was prolonged to about

TABLE 1.—EFFECT OF VARYING CONCENTRATIONS OF SODIUM CITRATE AND CALCIUM CHLORIDE ON PROTHROMBIN TIME OF NORMAL HUMAN PLASMA (MEAN OF TEN SERIAL EXPERIMENTS; PHOTOELECTRIC DETERMINATION)

Molar Concentration of Calcium Chloride	*Molar Concentration of Sodium Citrate*	
	0.1	*0.2*
0.01	20.4 seconds	211.5 seconds
0.02	13.2 seconds	31.1 seconds
0.04	16.3 seconds	16.5 seconds
0.08	22.5 seconds	20.7 seconds
0.16	68.1 seconds	66.1 seconds

TABLE 2.—EFFECT OF VARYING CONCENTRATIONS OF SODIUM OXALATE AND CALCIUM CHLORIDE ON PROTHROMBIN TIME OF NORMAL HUMAN PLASMA (MEAN OF TEN SERIAL EXPERIMENTS; NAKED EYE DETERMINATION)

Molar Concentration of Calcium Chloride	*Molar Concentration of Sodium Oxalate*	
	0.1	*0.2*
0.00125	39.7 seconds	120.0 seconds
0.0025	19.3 seconds	50.9 seconds
0.005	16.2 seconds	24.9 seconds
0.01	15.2 seconds	21.6 seconds
0.02	14.8 seconds	19.4 seconds
1.14	19.2 seconds	18.3 seconds
0.08	29.8 seconds	27.4 seconds
0.16	82.9 seconds	82.9 seconds

B. Effect of Concentration of Anticoagulant Solution upon Prothrombin Time of Hypoprothrombinemic Plasma. In another group of experiments the concentration of the anticoagulant solution to which hypoprothrombinemic blood was added, was reduced. The prothrombin time was determined with varying concentrations of calcium chloride. These experiments were carried out with two concentrations of sodium oxalate, namely, 0.1

21 seconds or more as obtained with commercial (Difco) thromboplastin. In any patient placed on dicoumarin the fluidity of the blood at lower (suboptimal) concentrations of sodium oxalate or sodium citrate was maintained, as the prothrombin time increased. The prothrombin time obtained with lower concentrations of calcium chloride and derived from blood suspended in 0.1 molar concentration of sodium oxalate increased considerably and progres-

sively as the prothrombin activity decreased. This "sensitivity to calcium" was almost nonexistent at lower concentrations of calcium chloride in the tube containing 0.025 molar solution of sodium oxalate (Fig. 2).

As seen from Fig. 2, the mean prothrombin time in a series of 20 dicoumarinized patients obtained with 0.00125 molar solution of calcium chloride increased from 27.5 seconds, when 0.025 molar solution of sodium oxalate was used to 120.0 seconds when 0.1 molar solution of sodium oxalate was employed. On the other hand, no notable difference was observed between the prothrombin times obtained with higher concentrations of calcium chloride, such as 0.08 molar solution with either concentration of anticoagulant solution. Furthermore, it was noted that the optimum prothrombin time decreased correspondingly with a lower molar concentration of anticoagulant solution. Whereas the mean optimum prothrombin time (Fig. 2) was 20.5 seconds as obtained with 0.1 molar solution of sodium oxalate the corresponding optimal prothrombin time obtained with 0.025 molar solution of sodium oxalate was only 18.0 seconds. In some cases the difference was as great as 9.6 seconds. The reduction of the concentration of the anticoagulant solution resulted in a shortening of the optimum prothrombin time in all instances. The magnitude of the reduction, however, was unrelated to the degree of hypoprothrombinemia.

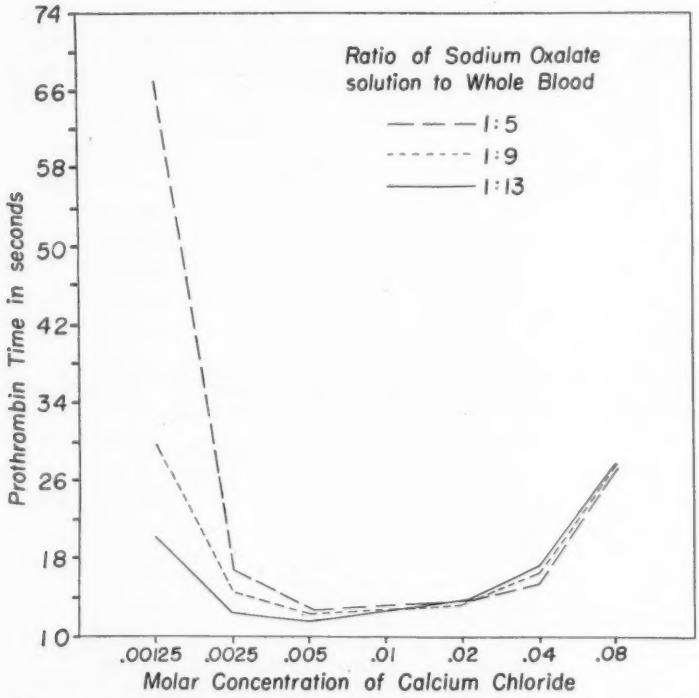

FIG. 1.—Effect of the Ratio SodiumOxalate/Normal Blood Upon Prothrombin Time.

Experiments in ten dicoumarinized patients utilizing 0.1 and 0.025 molar

concentration of sodium citrate as anticoagulant solution showed almost identical results as those obtained with sodium oxalate.

Discussion. The original concept of the one-stage Quick prothrombin determination has been based upon the assumption that "with the addition of a fixed quantity of calcium and an excess of thromboplastin prothrombin is the only variable and the clotting time of oxalated plasma under these conditions can be considered a direct measure of the prothrombin concentration of the blood"[5]. This thought has since been amplified inasmuch as prothrombin accelerators discovered after the advent of the two commonly used prothrombin methods also play an important role as variable factors in the process of coagulation[7]. The concentration of calcium has been known to be of great importance as shown by a number of investigators[1,2,6,8]. This fact has been borne out by the present study. In addition, the results of our experiments conclusively demonstrate that the concentration of the anticoagulant solution such as sodium oxalate or sodium citrate is of equal impor-

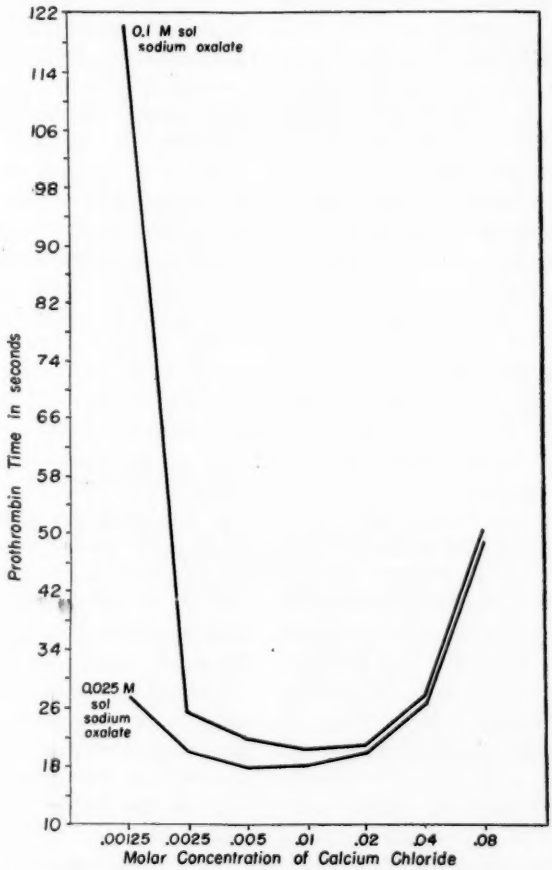

FIG. 2—Effect of the Ratio Sodium Oxalate/Hypoprothrombinemic Blood Upon Prothrombin Time.

tance for the determination of prothrombin time. It seems that a higher concentration of anticoagulant solution is associated with a marked increase of the sensitivity to a low concentration of calcium. In addition, the prothrombin time obtained with the optimum molar concentration of calcium, when a higher concentration of anticoagulant solution is used, also increases, thus closely simulating the findings encountered in hypoprothrombinemic plasma as after administration of dicoumarin (Fig. 2). It is of interest that, as seen from Table 1, the prothrombin time obtained from plasma added to 0.2 molar concentration of sodium citrate becomes unduly prolonged if 0.01 molar solution of calcium chloride is used as compared with a much lower concentration of calcium chloride (0.00125) when plasma is added to 0.2 molar concentration of sodium oxalate (Table 2). The study with citrated plasma, therefore, was not extended below calcium chloride concentrations of 0.01 molar solution.

These findings are amplified by another experiment in which the amount of anticoagulant solution has been increased relatively by reducing the amount of blood. The results thus obtained likewise demonstrate an increase of the sensitivity to a low concentration of calcium as well as a moderate increase of the optimum prothrombin time. An additional finding in this latter group of experiments is the fact that the prothrombin times are even less sensitive to a low concentration of calcium if a relatively smaller amount of anticoagulant solution is added to the blood specimen as shown by the curve derived from the specimen in which 13 parts of blood were added to 1 part of 0.1 molar solution of sodium oxalate (Fig. 1). A moderate reduction of the optimum prothrombin time also was encountered if the ratio of oxalate to blood was reduced to 1:13 and if a 0.005 molar solution of calcium chloride was employed.

From these experiments it can be concluded that sensitivity to a low calcium concentration as well as an increase of the optimum prothrombin time can be produced in normal plasma if the concentration of the anticoagulant solution is increased either in absolute terms, or relatively, by increasing the ratio of anticoagulant solution to blood.

The reverse phenomenon, namely, the reduction or abolition of sensitivity to low concentration of calcium has been demonstrated in hypoprothrombinemic blood by reducing the concentration of sodium oxalate. Whereas, euprothrombinemic blood readily coagulates if added to 0.025 molar solution of sodium oxalate in the conventional ratio of 9:1, hypoprothrombinemic blood with a sufficiently reduced prothrombin level will remain fluid if added to the same anticoagulant solution as shown previously[4].

The plasma obtained after addition of 9 parts of hypoprothrombinemic blood to 1 part of 0.025 molar solution of sodium oxalate contains considerably less of an excess amount of sodium oxalate than the plasma derived from the conventional procedure. As seen in Fig. 2 the prothrombin times obtained from the conventional specimen display a decided sensitivity to a low concentration of calcium. The prothrombin times obtained after addition of blood to 0.025 molar solution of sodium oxalate, however, do not show this phenomenon. Furthermore, a reduction of the optimum prothrombin time in the latter instance is noted as well.

The reduction of the prothrombin time upon addition of blood to 0.025 molar solution of sodium oxalate as

compared with the conventional method presents the problem whether the effect of dicoumarin is more than an actual reduction of the amount of prothrombin. From this study as well as from our previous investigation it seems that the reduction of the amount of prothrombin has a secondary effect, and that it creates an excess amount of anticoagulant solution. This, in turn, leads to a further prolongation of the prothrombin time. Thus, the optimum prothrombin time of 20.5 seconds as obtained with the conventional procedure (Fig. 2) seems to consist of 2 time components, the first amounting to 18.0 seconds (optimum prothrombin time obtained with 0.025 molar solution of sodium oxalate), representing the actual reduction of prothrombin, and the second component amounting to 2.5 seconds as caused by the presence of a relative excess of sodium oxalate in the specimen derived from the conventional procedure.

It may be concluded from this study that an inaccurate measurement, particularly a reduction of the quantity of anticoagulant solution, may result in a shortening of the prothrombin time in hypoprothrombinemic blood, thus leading to an erroneous estimation of the prothrombin level.

Summary and Conclusions. 1. Prothrombin times of normal plasma are influenced by the concentration of the anticoagulant solution.

2. Both an absolute and a relative increase of the concentration of the anticoagulant solution when added to normal blood produces

a) a sensitivity to low concentrations of calcium chloride, and

b) an increase of the "optimum prothrombin time."

3. The decrease of the concentration of the anticoagulant solution added to hypoprothrombinemic blood results in a decrease or abolition of the sensitivity to low concentrations of calcium chloride as well as a decrease of the "optimum prothrombin time."

4. Inaccurate measurement of the quantity of anticoagulant solution may lead to erroneous estimation of the prothrombin level.

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SMALL VESSEL DYSFUNCTION IN PATIENTS WITH DIABETES MELLITUS. I. Skin Temperature Response to Priscoline in the Toes of Diabetics*

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The vasodilatory effects of Priscoline on the vessels of the extremities were definitely established by Grimson, Reardon, Marzoni and Hendrix[1] who have reviewed the American and European literature concerning both the pharmacological and clinical properties of the drug. The last workers[2] reported that the skin vasodilatation obtained in patients receiving doses ranging from 0.5 to 1 mg. per kilo is due to a histamine-like action on small vessels, whereas the effect after larger doses, 2 to 3.5 mg. per kilo, is due to a block of the augmentor sympathetic vascular receptors and adrenolysis. A recent study by Murphy *et al.*[5] concerning the effects of small doses (25 mg.) of Priscoline on the blood flow to the extremities of healthy adults demonstrated that after intravenous administration of the drug the skin temperature in all patients rose maximally (2° to 5° F.) within 5 minutes, returning to normal by 15 minutes. They also found an overall increase in blood flow to the limb as determined by the venous occlusion plethysmograph. By testing the removal of radioactive sodium from the gastrocnemius muscle, it appeared that the blood flow to the muscles was decreased. Wakim *et al.*[7], using larger doses (50 mg.) of Priscoline, found much greater and much more sustained responses than the former workers in all the tests used, but they did not make observations concerning muscle blood flow; this work will be discussed later.

The present study was undertaken after it was noted clinically that several diabetic patients with peripheral arteriosclerosis obliterans had marked improvement in their symptoms of intermittent claudication after Priscoline therapy using larger doses, and yet tests of the skin temperatures of the feet showed no or little elevation after the medication. This suggested that improvement could occur in the circulation to the muscles without evidence of improvement in skin circulation. Clinically, a similar situation is often seen in patients with diabetes mellitus who have superficial gangrene of the toes, and yet they have excellent pulsations of the arteries in the feet and never had symptoms suggestive of diminished circulatory efficiency in the extremities. This has recently been re-

* This study was supported by a grant from Ciba Pharmaceutical Products, Inc.

emphasized by Kramer[3], who has proposed the name endarteritis obliterans for this type of case in which the small vessels are at fault (both in diabetics and non-diabetics) in contradistinction to arteriosclerosis obliterans, where the larger vessels are involved.

Methods. Patients from the Diabetic Clinic of the Long Island College Hospital were chosen for this study if they had no complaints referable to their legs. Most of them were patients who had had diabetes for 10 to 15 years. They all had excellent dorsalis pedis and posterior tibial pulsations. All had warm feet with normal color in dependency and on raising. Clinically they were judged to have normal peripheral circulation. Since these diabetic patients came from a clinic population which was in the older age groups, a similar series of non-diabetic patients was chosen from the wards of the Long Island College Hospital to serve as controls.

All patients were kept on a cot in a large room without drafts in which the room temperature remained constant between 60° to 62° F. The patients were wrapped in several blankets with only their feet protruding. They were tested in this fashion until the temperature of the skin of the toes became constant; this took variably from ½ to 1 hour. The arm was then exposed only long enough to give 2 cc. (50 mg.) of Priscoline intravenously over a period of 60 seconds. Most patients felt a warm sensation in the face, traveling down the body until the feet felt warm. The sensation of warmth was even felt by the "non-reactors". Many complained of stuffiness of the nose which was annoying in the cold room and often led to shortening of the experimental period. Thermocouple readings were made at 5-minute intervals on the halluces of both feet and recorded.

Results. In all, 30 patients were studied and the temperature results are recorded as the number of degrees (F.) rise above the control value following Priscoline administration. In Table 1 are the results obtained in 14 patients without diabetes, convalescing from various diseases. Patients 12 and 13 had marked cardiac failure and showed marked impairment in the peripheral vascular response to the Priscoline such as is demonstrated in patients with cardiac failure by other methods[6]. Patient 14, having tabes dorsalis with trophic leg changes, also showed no vasodilatation after the Priscoline administration. The poor temperature response of these patients gave an arbitrary standard by which other cases with poor responses could be judged, namely, the skin temperature of the toes did not rise above 5° F. within 30 minutes. Of the remaining 11 patients who had no complications in which peripheral vascular changes would be expected, only 1 had such a poor response. On the other hand, among the 16 diabetics recorded in Table 2, 7 patients (over 40%) demonstrated poor vasodilatation after 50 mg. of Priscoline was given intravenously. No correlation could be made out between the vascular dysfunction and the severity or degree of control of the diabetes.

Discussion. The decreased skin vessel dilatation after Priscoline in the toes of a large percentage of diabetics who had no clinical suggestion of peripheral vascular disease or of neuropathy suggests that a dysfunction of the small cutaneous vessels can exist independent of the condition of the larger vessels. It also casts doubt on the value of using skin temperature responses in evaluating the circulatory efficiency of the extremities of diabetics.

Similar evidence of small vessel dysfunction in the extremities of patients with diabetes mellitus has been demonstrated by other workers using different techniques. Starr[6] in 1930 employed the intracutaneous histamine flare test on the legs of stabilized diabetics and found that in 50 patients without any evidence of arteriosclerosis, 17 showed moderately diminished and 8 cases showed markedly diminished wheal tests. In another group of 25 patients with evidence of generalized arteriosclerosis but with excellent dor-

salis pedis pulsations, 9 had moderately diminished and 11 had markedly diminished wheal responses to the locally administered histamine. Starr believed that neurogenic influences were absent in these cases because neuritis influences the flare rather than the wheal in histamine tests.

More recently, Megibow *et al.*[4] also found changes in circulation in the small vessels of the extremities in 10 out of 53 diabetic patients in whom no clinical evidence of peripheral vascular disease could be demonstrated. These workers measured the oscillometric index as well as venous occlusion plethysmographic changes by means of a photoelectric microplethysmograph before and after the administration of nitroglycerine or tetraethylammonium.

TABLE 1.—SKIN TEMPERATURES OF TOES BEFORE AND AFTER PRISCOLINE IN 14 NON-DIABETIC PATIENTS

Room Temp. 60–62° F. Priscoline (50 mg.) given intravenously. (RH—right, LH—left hallux)

Patient No.	*Age (yrs.)*	*Disease*		*Maximum Temperature Readings (above control value)* 5 to 10 min.	15 to 20 min.	20 to 30 min.	*Response*
Convalescent Patients							
1.	40	Mucous Colitis	R.H.	1½°	10°	12½°	
			L.H.	1°	14½°	15°	Good
2.	64	General A.S.	R.H.	½°	10°	10½°	
			L.H.	0°	5½°	6½°	Fair
3.	55	Pyelonephritis	R.H.	4½°	13°		
			L.H.	5½°	13½°		Good
4.	45	Duod. Ulcer	R.H.	16°	20°	12°	
			L.H.	12°	18½°	14½°	Good
5.	56	Hodgkin's Dis.	R.H.	13°	14°		
			L.H.	14°	16°		Good
6.	45	None	R.H.	2°	4½°	10°	
			L.H.	3½°	8½°	12°	Good
7.	51	Cirrhosis	R.H.	6½°	8½°		
			L.H.	5°	6½°		Fair
8.	61	Post-Pneumonia	R.H.	9½°	11½°		
			L.H.	6½°	8°		Fair
9.	25	Student	R.H.	13°	11½°		
			L.H.	9°	8°		Fair
10.	46	Cirrhosis	R.H.	1°	7½°	8°	
			L.H.	1°	3°	5°	Poor
11.	45	Aortic-ins. Rheumatic	R.H.	9°	16½°	20°	
			L.H.	12°	20°	21°	Good
Cardiac Failure and Tabes							
12.	66	A.S.H.D.	R.H.	−2°	−2½°	−2°	
			L.H.	−2½°	−3½°	−3°	Poor
13.	56	Luetic Aortitis	R.H.	2°	2°	2°	
			L.H.	2½°	4°	4°	Poor
14.	52	Tabes	R.H.	½°	2½°	4°	
			L.H.	−1½°	−2°	−1°	Poor

Since the blood flow in the extremities was found to be diminished in these 10 patients although the oscillometric indices were normal, it was concluded that the vascular damage is localized in the arterioles and capillaries.

It would appear that in addition to the occurrence of well recognized "small vessel disease" in the retina and kidneys of diabetics, this type of vascular damage also occurs in the extremities of diabetics. Many of the instances

TABLE 2.—SKIN TEMPERATURES OF TOES BEFORE AND AFTER PRISCOLINE IN 16 DIABETICS

Room Temp. 60–62° F. Priscoline (50 mg.) given intravenously. (RH—right, LH—left hallux)

Patient No.	*Age (yrs.)*	*Diabetes*	*Complication*		*Maximum Temp. Readings (above control)* 5–10 min.	15–20 min.	25–30 min.	*Response*
1.	59	Mod. severe good control		R.H. L.H.	2° 9°	8° 12½°	4½° 9½°	Fair
2.	57	Mild good control		R.H. L.H.	15° 18½°	17° 24°	17° 24°	Good
3.	55	Mod. severe good control		R.H. L.H.	9° 13°	10° 13½°	11° 13°	Good
4.	40	Very severe poor control	Retinopathy	R.H. L.H.	5° 6°	13° 17°	15½° 18°	Good
5.	51	Mild good control	Retinopathy	R.H. L.H.	½° −1½°	17½° 16°	15° 19°	Good
6.	42	Severe poor control		R.H. L.H.	11½° 10½°	21½° 22½°	23° 25°	Good
7.	58	Mild good control	Hypertension Coronary A.S.	R.H. L.H.	0° 1°	8½° 4°	14° 8½°	Good
8.	57	Mild poor control		R.H. L.H.	18½° 4½°	18¼° 12°	19½° 18°	Good
9.	63	Mod. severe poor control		R.H. L.H.	14° 15°	20° 23°		Good
10.	65	Mild good control	Leukemia	R.H. L.H.	−2° −4°	−1½° −4°	−3° −4½°	Poor
11.	69	Mild poor control		R.H. L.H.	4° 2°	3½° 2°	5½° 1°	Poor
12.	56	Severe good control	Retinopathy	R.H. L.H.	0° −1°	1° 0°	1° 0°	Poor
13.	59	Mild good control		R.H. L.H.	4° 1½°	3° 2°	3° 2°	Poor
14.	62	Mild good control	Hypertension	R.H. L.H.	1½° 1°	3½° 4½°	5° 5°	Poor
15.	58	Mild good control	Retinopathy	R.H. L.H.	½° 0°	½° ½°	½° 0°	Poor
16.	54	Mild poor control		R.H. L.H.	0° 1½°	3½° 1½°	5° 1½°	Poor

of superficial gangrene seen in diabetics following minor trauma even in the presence of "good" peripheral circulation, as judged clinically, may be secondary to this small vessel disease in their extremities.

The data reported by Wakim *et al.*[7], concerning the effect of a 50-mg. dose of Priscoline given intravenously to 5 patients with multiple sclerosis and 5 patients with migraine, are very complete. A perusal of the data concerning the first 5 cases shows that an increase in blood flow as determined by the venous occlusion plethysmograph was often much greater than the simultaneously determined increase in the skin temperature, corroborating our clinical observations mentioned in the introduction that Priscoline increases the blood flow to the limbs even when maximum skin vasodilatation is not obtained.

In the title of this paper, the term "small vessel dysfunction" was used because no evidence is at hand concerning whether a pathological change exists in the skin vessels or whether a neurovascular dysfunction prevents the vasodilatation. Since the dosage of Priscoline used in this study is considered by Hendrix *et al.*[2], to cause vasodilatation through its histamine-like action, further studies are needed to clarify the role that neurological influences may play.

Conclusions. (1) In a large percentage of patients with diabetes mellitus, there is an inability of the skin vessels of the toes to dilate maximally, as measured by skin temperature determinations following intravenous Priscoline administration.

(2) This small vessel dysfunction exists in the presence of clinically normal peripheral circulation.

(3) The improvement in peripheral circulation in many patients with diabetes mellitus following the use of a vasodilator like Priscoline cannot be evaluated by skin temperature readings alone.

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SMALL VESSEL DYSFUNCTION IN PATIENTS WITH DIABETES MELLITUS: II. RETINAL VESSEL RESPONSE IN DIABETICS FOLLOWING PRISCOLINE*

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In a previous study, the authors[4] found that there was a diminished vasodilatory response in the skin vessels of the toes in a large number of older diabetics who had normal peripheral circulation as judged by clinical standards. This was demonstrated by skin temperature studies following intravenous Priscoline, and the work confirmed other published studies[6,7] employing different tests, that such a dysfunction of the smaller vessels of the extremities exists in diabetic patients. It seemed important to determine whether a similar lack of vasodilatation in small vessels occurs in diabetes in other organs; this study was planned to investigate the retinal vessels.

Direct measurement of the degree of dilatation of retinal vessels is difficult but an indirect method, angioscotometry, is relatively simple to perform. Angioscotometry is the method of tracing out bands of physiologic blindness corresponding to the retinal blood vessels[2]. This has been carefully studied by Evans[3] who demonstrated that the perivascular lymph spaces as well as the retinal vessels are represented geographically on the angioscotoma. Slight dilatation of the retinal vessels interferes with proper lymph drainage and causes a disproportionately marked widening of the angioscotoma. The present authors[1] studied the effect of intravenous Priscoline (50 mg.) on the angioscotoma of healthy adults and patients with various vascular complications. Marked widening of the angioscotoma occurred in the healthy controls as well as in a series of patients with essential hypertension, patients with hypertension due to renal disease, and patients with moderate retinal vessel sclerosis. Only in those cases with an extreme degree of retinal sclerosis was there relatively no widening of the angioscotoma following intravenous Priscoline. The present study was planned to make further observations in patients with diabetes mellitus.

Methods. Twenty-seven patients with diabetes mellitus were selected in the Long Island College Hospital and Diabetes Clinic. An attempt was made to choose those whose

* This study was supported by a grant from Ciba Pharmaceutical Products, Inc.

illness was of long duration and who had little retinal vascular sclerosis. Their ages varied from 18 to 69 years, and the duration of the diabetes from 6 months to 30 years. Careful ophthalmoscopic notes were made concerning the retina and the retinal vessels in each patient. The angioscotoma was mapped employing the Evans Stereocompimeter and charts, using a white spherical test object which was 0.4 mm. in size. The illumination was 15 foot-candles and monocular fixation was used. The blind spot was first outlined and then the object was moved around until the superior arched angioscotoma was located and plotted. The patients were then given 50 mg. Priscoline intravenously over a period of 60 seconds and the angioscotoma was replotted at short intervals. The maximum widening usually occurred within 15 to 20 minutes. The test was conducted for at least 45 minutes after the Priscoline was given. The widening of the angioscotoma was classified as previously described:

good, if the band was 4.0° or more in width; fair, if the band was between 1½° and 4° in width; and poor, if the band was no more than 1½° in width.

Results. The results are recorded in Table 1. In 12 of the 28 patients studied, there were poor vasodilatory responses to the intravenous Priscoline. Included in Table 1 are the findings in the eye grounds of the patients studied. It can be seen that excellent vascular responses were obtained even in the presence of early diabetic retinopathy as manifested by the typical punctate aneurysms. In 11 out of the 12 cases showing poor responses, perimacular hard exudates were present. Poor responses could not be correlated with other findings of diabetic retinopathy.

TABLE 1.—RETINAL VESSEL DILATATION AFTER PRISCOLINE AS MEASURED BY ANGIOSCOTOMETRY IN 28 DIABETICS

Patient	*Age (yrs.)*	*Angioscotoma Dilatation Following Priscoline*	*Vessel Sclerosis*	*Ophthalmoscopic Picture*		
				Punctate Aneurysms	*Flame Hemorrhages*	*Perimacular Hard Exudate*
(1)	18	Good	0	+	0	0
(2)	25	Good	0	0	0	0
(3)	31	Fair	0	+	0	0
(4)	38	Poor	0	+	0	*++
(5)	39	Poor	0	+	0	++
(6)	40	Poor	0	+	0	+
(7)	46	Poor	0	+	0	+
(8)	51	Good	0	0	0	0
(9)	51	Good	0	0	0	0
(10)	52	Good	+	+	0	++
(11)	53	Good	+	0	0	0
(12)	54	Good	0	++	0	0
(13)	54	Good	0	+	0	0
(14)	54	Poor	0	0	0	++
(15)	54	Poor	+	+	0	0
(16)	56	Fair	0	0	0	0
(17)	56	Poor	0	++	+	++
(18)	57	Poor	+	+	+	++
(19)	60	Poor	+	++	+	++
(20)	61	Fair	0	+	0	0
(21)	61	Good	+	0	0	0
(22)	61	Poor	+	++	0	++
(23)	63	Good	0	+	0	0
(24)	66	Poor	++	0	0	++
(25)	66	Good	0	++	0	0
(26)	68	Poor	+	++	0	+
(27)	69	Fair	++	+	+	0
(28)	81	Fair	+	+	0	0

* Patient also had fluffy exudates

Comment. Previously[1] it was shown that only patients who had *advanced* retinal sclerosis showed a *poor* widening of the angioscotoma following intravenous Priscoline. In the present study it was found that in a large number of diabetics a similar phenomenon occurred, despite the absence of ophthalmoscopic evidence of any significant vascular sclerosis. Thus there seems to be an inability of the smaller vessels in the retina of diabetics to dilate, similar to the dysfunction previously found in the skin vessels of the toes of diabetics. Six of the patients in this series had parallel studies on the temperature responses of their toes as well as angioscotoma responses to intravenously administered Priscoline. Patients 6, 14, and 18 had poor widening of the angioscotoma, yet had excellent temperature responses in the toes following intravenous Priscoline. Patient 17 had poor responses in both tests, while patients 13 and 23 had poor peripheral vascular dilatation with excellent angioscotoma widening. The "small vessel dysfunction" was not generalized in these instances.

Recent studies by Krasno and his co-workers[5] employing the flicker photometer have shown that vasodilators, such as nitrites, fail to effect vasodilatation of the retinal vessels in the presence of arteriosclerosis, myocardial failure and coronary artery disease. In the present work it was attempted to eliminate patients with these complications so that the results would only reflect a diabetic complication. That the lack of vasodilatation response in the retinal vessels is of diabetic etiology is further suggested by the fact that all but one of the "poor responders" had diabetic type of exudates in the eyegrounds. The clinical significance of this is being further studied by one of us (M.C.) and the results will be reported in the future.

Summary. (1) In many diabetics without ophthalmoscopic evidence of significant retinal arteriosclerosis, there is an inability of the retinal vessels to dilate maximally after intravenous priscoline administration, as determined by poor widening of the angioscotoma.

(2) This fault is accompanied by exudation in the perimacular region.

(3) There is no correlation between such "small vessel" dysfunction in the retinal vessels and that shown to occur in the skin of the toes of patients with diabetes.

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EFFECTS OF HYDROGENATED ALKALOIDS OF ERGOT ON VASOMOTOR REFLEXES

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Considerable advancement has been made in our knowledge of ergot and its alkaloids, both natural and hydrogenated, during the past 43 years. Through chemical alteration of the natural alkaloids of ergot, the hydrogenated alkaloids have been derived which retain a sympatholytic vasodilating action but no longer manifest the direct acting vasoconstrictive effects[2,14]. Thus, ergot in the hydrogenated form might have a place in the treatment of hypertension and peripheral vascular disease where a medical sympathectomy is desirable. Robert H. Goetz[8] reported favorable results in hypertension using one of these alkaloids, dihydroergocornine, parenterally. Similar results in hypertension have been reported by Von Kappert[11] using CCK 179, when administered by the combined oral and parenteral routes. It is the purpose of this report to determine if the sympathetic nervous system of hypertensive subjects can be significantly inhibited with this drug.

Methods and Materials. Eighty individuals were studied; 69 had hypertension, of these 62 had the essential benign type, 5 the arteriosclerotic type and 2 hypertension due to renal disease. Eleven were normal. The methods employed have been described in detail elsewhere[16]. Plethysmograms were recorded, using the Burch plethysmograph[4], and relative blood flow was measured, using the venous occlusion technique with the occluding cuff at ankle or wrist. Skin temperatures were recorded electronically every 15 seconds with a 4-point Brown recorder. Blood pressures were recorded with the Lange sphygmotonograph[13], venous pressures were taken with the phlebomanometer[5] and oscillometric readings were made with the Collens-Wilensky oscillometer. Skin resistance and galvanic reflex were studied with the Lafayette psychogalvanometer. For all studies CCK 179* was given orally in 1.0 mg. tablets or intravenously in selected cases. This drug contains equal parts of dihydroergocornine, (DHO 180) C_{31} H_{41} O_5 N_5, dihydroergocristine (DCS 90) C_{35} H_{41} O_5 N_5, and dihydroergokryptine (DHK 135) C_{32} H_{43} O_5 N_5.

Results. The acute depressor effect following medication with CCK 179 was studied in 6 individuals with essential benign hypertension, 2 with arteriosclerotic type hypertension, and 2 with arteriosclerotic obliterative disease of the lower extremities (Table 1). In the supine patient, a 20% decrease in systolic pressure and a 14% decrease in the diastolic pressure occurred in all cases 10 minutes after the injection of 1 mg. of the drug and continued at this level for 30 minutes. If the patient then assumed the erect position, a further fall in systolic pressure greater than 10% occurred in 66% of the patients, and a similar fall in diastolic pressure occurred in 50% of patients. These same patients received 1 cc. of normal saline solution intravenously on the following day and

* Supplied by Mr. Harry Althouse of the Sandoz Company. CCK 179 is known as Hydergine.

arterial pressure readings were made before, after 10 minutes, at 30 minutes, and after standing. Their values averaged 208/120, 211/122, 210/120, and 214/128, respectively. Considerable variation in the depressor effect in the same individual was observed after repeated intravenous administrations of similar doses of the drug (J. C., Table 1). This variability has been noted by others and may be due to the variable mechanisms responsible for an elevated arterial pressure. For example, neurogenic factors may be inhibited while the humoral mechanisms may be influenced little. The hypotensive effect of the drug with the patient in the standing position is shown as follows: Three milligrams were given orally to a 70-year old patient with essential benign hypertension (Figure 1). The patient had been examined approximately 20 times in the previous 6 months and the lowest arterial pressure obtained was 185/110 and the highest 260/155. The pressure taken for a 1½-minute period immediately before the drug was administered averaged 212/125. One hundred and five minutes after the drug, the pressures taken over a 4-minute period averaged 112/80. At 120 minutes, the systolic pressure measured over a 2-minute period averaged 125 mm. Hg, representing a beginning return toward the control level. On the following day this patient stood for a similar time after a placebo and the arterial pressure changed from 218/125 to 198/120. One 45-year old female with essential benign hypertension of moderate severity, who remained erect until collapse occurred, showed a definite hypotensive effect after 3.0 mg. of the drug orally (Fig. 2). Syncope occurred with hypotension and unconsciousness after 60 minutes. The arterial pressure returned toward normal shortly after assuming the horizontal position. The following day this patient remained erect for 60 minutes after a placebo. The blood pressure changed from 170/110 to 165/112. One 33-year old male with hypertension due to subacute glomerulonephritis and 4 plus albumin in the urine, exhibited an arterial pressure of 170/110 in the erect

TABLE 1.—ACUTE EFFECTS ON BLOOD PRESSURE AFTER INTRAVENOUS INJECTION OF 1 MG. OF CCK 179 WITH THE PATIENT IN THE SUPINE POSITION

Name	*Age*	*Diagnosis*	*Before*	*10 min. after Drug*	*30 min. after Drug*
T.	48	EBH	205/140	160/120	160/120
R. G.	42	EBH	200/130	160/110	168/128
G.	75	AH	192/100	130/50	140/55
A.	65	AOD	195/110	170/90	170/90
J. C.	35	EBH	250/142	210/136	212/140
			250/140	238/138	248/137
			220/129	159/115	158/112
			220/124	148/105	150/110
			210/140	192/132	200/132
			210/140	190/130	192/130
B.	46	AH	170/78	100/70	140/72
T.	65	EBH	300/160	220/100	230/103
S.	50	EBH	220/130	170/112	168/112
R.	55	EBH	165/105	135/90	138/92
G. C.	68	AOD	150/68	140/64	165/70
Mean			210/122	168/104	176/107

EBH—Essential Benign Hypertension
AH—Arteriosclerotic Hypertension
AOD—Arteriosclerotic Obliterative Disease
TAO—Thromboangiitis Obliterative Disease

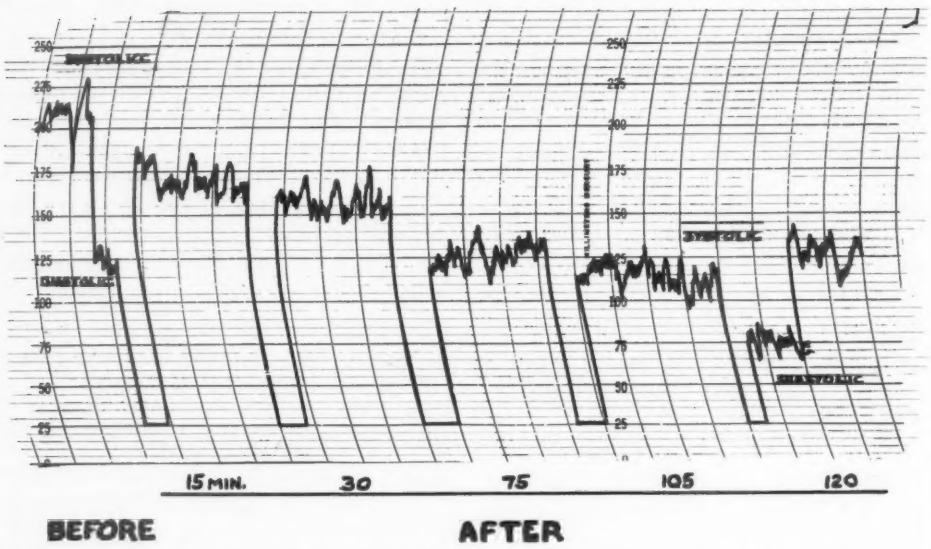

FIG. 1.—Influence of 3 mg. of CCK 179 given orally on blood pressure in an elderly patient with essential benign hypertension. The patient was in the standing position. A 47% reduction in systolic pressure and a 36% reduction in diastolic pressure were seen after 105 minutes.

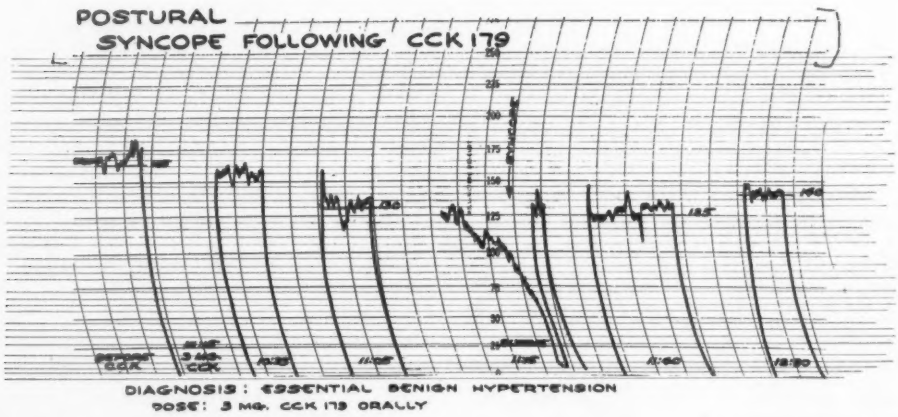

FIG. 2.—Influence of 3 mg. of CCK 179 given orally on the blood pressure of a 45-year old female with mild essential benign hypertension. The patient stood for the first portion of the test until syncope occurred. The blood pressure before the drug was 165 mm. of Hg systolic. Fifty minutes later the pressure was 130 mm. Hg systolic. One hour later the blood pressure fell precipitously, the patient became pale, and she fell to the floor semiconscious. The pulse rate and blood pressure were imperceptible when first tested. The legs were elevated and aromatic spirits of ammonia was inhaled. Twenty minutes later the systolic blood pressure was 125 in the supine position, and 75 minutes after the syncope, the pressure was 145 mm. systolic with the patient still supine.

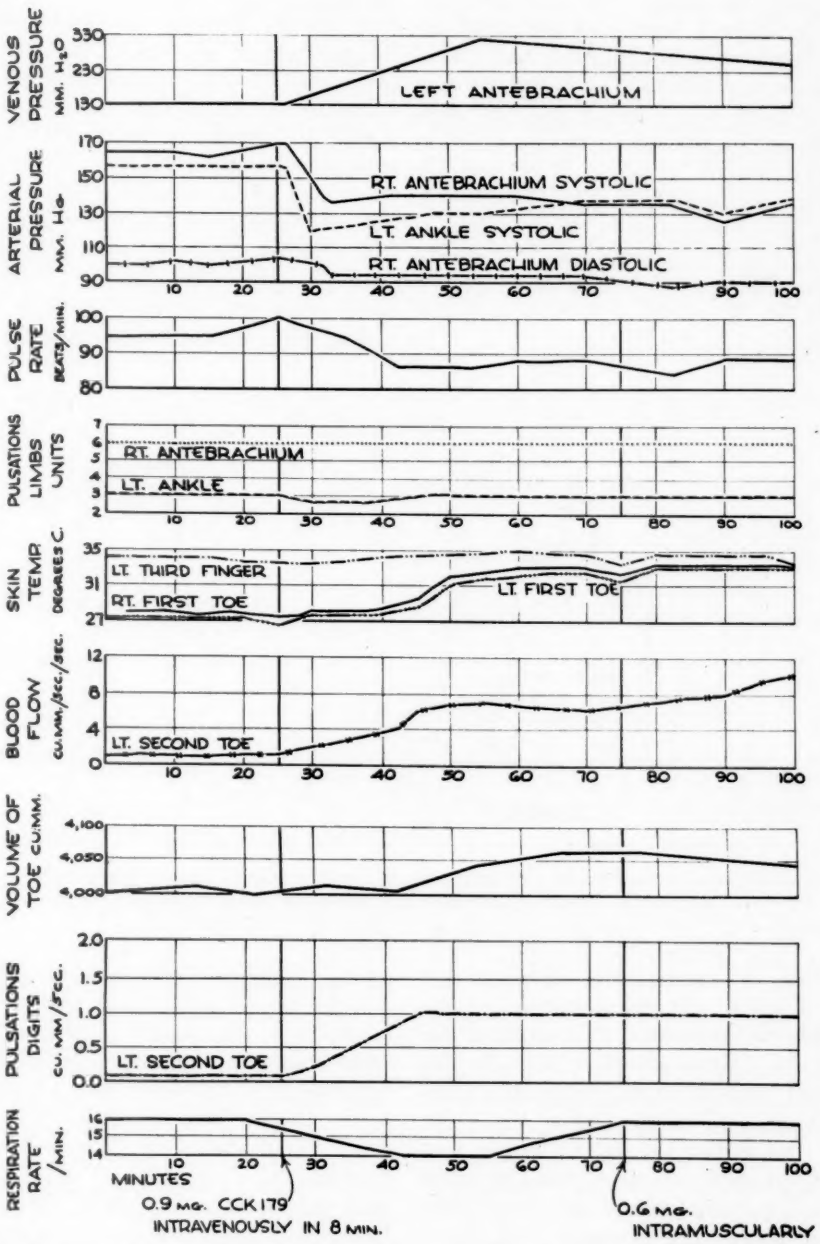

FIG. 3.—Systemic effects of CCK 179 given intravenously in a normal subject. These findings indicate a decrease in peripheral resistance (see text).

position before 3.0 mg. of the drug was administered orally. The pressure fell to 120/78 in 1 hour and remained at this level for 4 hours. At 5 hours the pressure was 135/85. The following day this patient was given a placebo and remained in the erect position for a similar length of time. The arterial pressure changed from 174/110 to 162/113. Ten other patients, studied under similar conditions, with the drug given orally, did not demonstrate a significant fall in systolic and diastolic pressures.

dicate a decrease in peripheral resistance as shown by a) a lowering of the arterial pressure accompanied by an increase of the venous pressure, b) a decrease in arterial pressure with an increase in digital flow, and c) a decrease in arterial pressure with an increase in the total volume of the digit. Evidence of decreased peripheral resistance persisted for the subsequent 100 minutes. Skin temperatures of the toes changed from 28 to 33°C., but subsequent studies on the same individual after a) a posterior tibial novo-

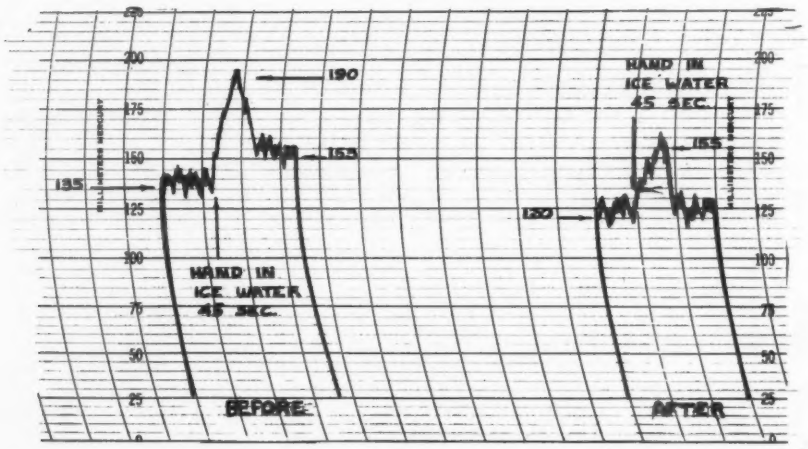

FIG. 4.—Cold pressor reaction in a 62-year old male with essential benign hypertension. A 36% reduction in systolic pressure was noted following CCK 179.

Mode of Action. The effect of 0.9 mg. of CCK 179 intravenously on the *peripheral resistance* in a normal 24-year old male is shown in Fig. 3. The arterial pressures recorded at the antebrachium and at the ankle, the pulse rate, the pulsations at the ankle, and the respiration rate all decreased, while the skin temperatures of the digits, blood flows, total volume and pulsations of the toes, and the antecubital venous pressures increased. The changes began within 5 minutes of the drug administration. These findings incaine block, b) body heating using 2 double size electric pads and 2 wool blankets for 45 minutes, and c) tetraethylammonium chloride, 500 mg. intravenously, revealed skin temperatures of the toes of 35.5, 36.0, and 36.0° C., respectively. Thus, the relative degree of peripheral vasodilation was not great using CCK 179. Likewise, CCK 179 produced a definite increase in the blood flow from 1.0 to 10.0 c. mm. per second in the subject illustrated in Fig. 3. However, tibial block, body heating, and TEAC in-

creased the toe flow on other occasions to 25.0, 36.0 and 35.0 c.mm. per second, respectively. Thus the relative increase in toe flow due to CCK 179 was not great. Similarly, the pulsations at the toe with CCK 179 increased from 0.1 before to 1.0 c. mm. after administration of the drug, whereas with the tibial block, body heating or TEAC, the pulsations reached 8.0, 12.0 and 10.0 c. mm., respectively. It was thus concluded that the peripheral vasodilating properties of 0.9 mg. of the drug administered intravenously in a normal subject were mild as compared to other peripheral vasodilating procedures.

TABLE 2.—EFFECT OF CCK 179 ON VASOMOTOR REFLEXES OF FINGER TIP

				Blocking of Reflex at Finger		
Name	*Age*	*Diagnosis*	*Dose Mg.*	*Inspiration*	*Sound*	*Cold*
W.	55	EBH	2.0 orally	0	0	0
L.	55	EBH	2.0 "	0	0	0
S.	69	EBH	2.0 "	0	0	0
T. W.	35	Normal	3.0 "	0	0	0
A. W.	43	TAO	4.0 "	0	0	0
L.	55	EBH	0.3 IV	Partial	Partial	Partial
T.	65	EBH	0.3 "	"	"	"
W.	43	TAO	0.6 "	Complete in 10 min. Partial in 30 min.	Complete in 10 min. Partial in 30 min.	"
P.	34	TAO	1.0 "	Complete in 10 min. Partial in 40 min.	Complete in 10 min. Partial in 40 min.	"
P.	19	Normal	1.0 "	Complete in 10 min. Partial in 45 min.	Complete in 10 min. Partial in 45 min.	Complete in 10 min. Partial in 45 min.

The *cold pressor reaction* on the systolic pressure produced by placing the hand and arm in ice water for 60 seconds was recorded in 5 individuals with essential benign hypertension. One hour after 3.0 mg. of the drug were administered orally, the vasopressor reaction was reduced 30 to 58%, average 40%. These results are similar to those obtained by Freis *et al.*[7]. An example of the vasopressor reaction before and 50 minutes after 3.0 mg. of the drug were given orally to a 62-year old male with mild essential benign hypertension is shown in Fig. 4. Before CCK 179, placing the hand in ice water caused the systolic pressure to rise from 135 to 190 mm. One hour after 3.0 mg. of CCK 179 orally, the same test elevated the pressure from 120 to 155. Thus, the cold pressor response was reduced 36%. This suggests an inhibitory effect on the sympathetic nervous system which may explain the subjective improvements of many of the patients. It is possible that this drug produces a regulating effect on the pressure, suppressing the sudden rises in pressure which may be responsible for headache, palpitation, and other symptoms.

Inhibition of certain *induced vasomotor reflexes* at the finger tip were studied in 2 normal subjects, 5 patients with essential benign hypertension, and 3 with thromboangiitis obliterans, one of whom showed the Raynaud's phenomenon (Table 2). The vasomotor reflexes were not blocked by 4.0 mg. of the drug orally. There was a partial blocking when 0.3 mg. was given intravenously. Progressively greater blocking when 0.3 mg. was given intra-

venously. Progressively greater blocking resulted from 0.6 to 1.0 mg. of the drug administered intravenously. Inhibition of the inspiratory reflex at the finger tip in a normal individual 10 and 60 minutes after administration of 0.9 mg. of CCK 179 intravenously is after injection showed the reflex to be inhibited, which represents an inhibitory effect of the drug on the sympathetic system. The increase in the amplitude of pulsations of the finger as well as the increase in flow after administration of the drug also suggests

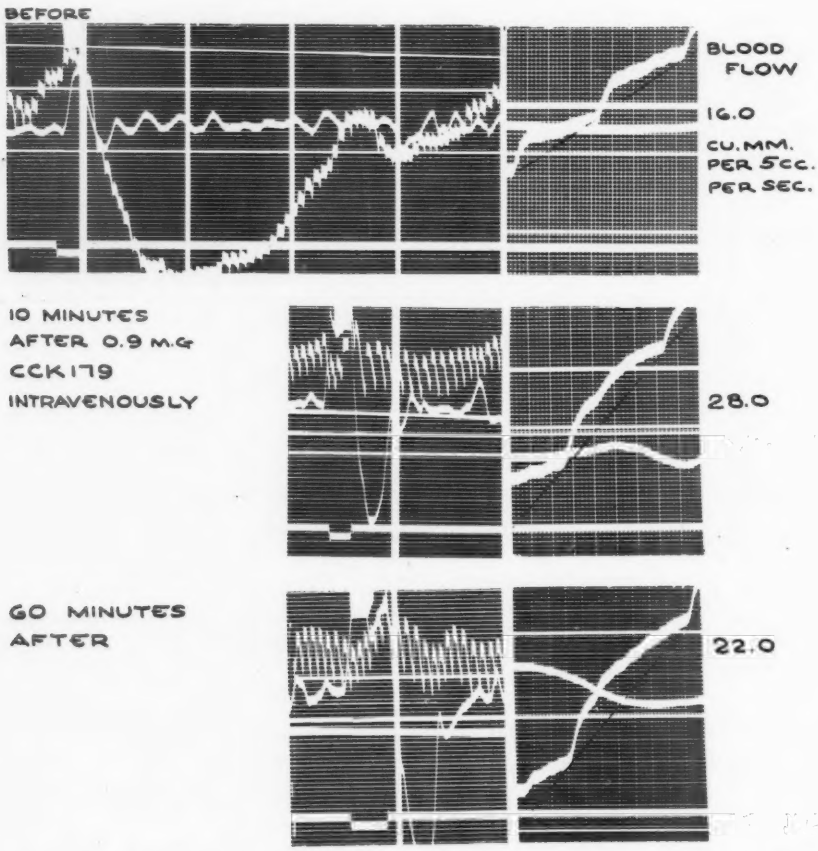

FIG. 5.—Blocking of the inspiratory reflex of a normal subject after CCK 179 was given intravenously. There is also an increase in the amplitude of pulsations and an increased digital flow.

shown in Fig. 5. Before the drug was given, inspiration resulted in a decrease in the volume of the finger of 55 c.mm. with a return to its previous volume in approximately 1 minute. This is due to a transient increase in sympathetic tone associated with deep breathing. Records made 10 and 60 minutes this same mechanism. The inspiratory and other induced vasomotor reflexes were studied in a 34-year old female with Raynaud's phenomenon associated with thromboangiitis obliterans (Fig. 6). There are definite vasoconstrictive responses to inspiration (Fig. 6B), expiration (Fig. 6C), sound of a buzzer

(Fig. 6D), and light directed into the eye (Fig 6E) prior to administration of the drug. Fifteen minutes after 1.0 mg. was injected intravenously the vasoconstrictive responses to these stimuli were absent. The blood flow to the finger tip more than doubled. Similar results were obtained 2 months after a cervical sympathectomy.

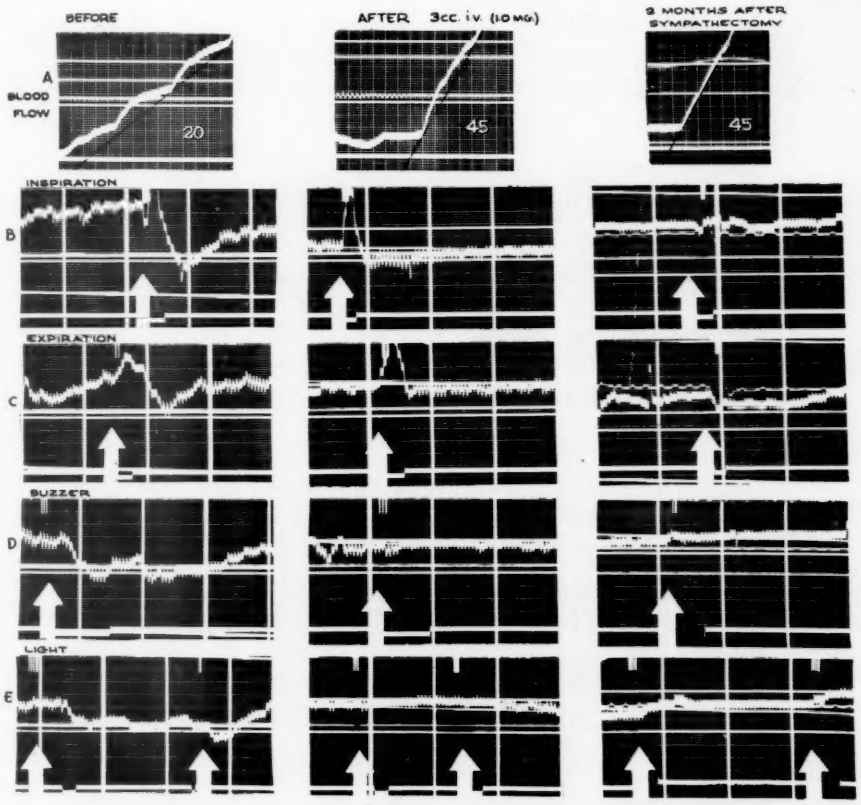

FIG. 6.—Inhibition of the vasomotor reflexes of the finger tip in a patient with thromboanglitis obliterans following administration of CCK 179 and cervical sympathectomy. There is an increase in the flow with each procedure. White arrow indicates when stimulus was given.

Modification of the spontaneous vasomotor activity with CCK 179 is shown in Fig. 7A-7B. One milligram of CCK 179 was injected intravenously and the spontaneous waves occurring at the finger tip of a 24-year old normal male were recorded. Spontaneous waves were present before the drug was given and were greatly reduced 15 minutes after injection. This indicates at least partial blocking of the sympathetic nervous system either centrally, along its course, through ganglia, or peripherally. Studies by others suggest a central depression of the sympathetic center in the hypothalamus[11,14]. The spontaneous waves were also studied in the same subject after 100 mg. of SC 1950 (2,6 dimethyl-diethyl-piperidinium bromide) intravenously for comparative purposes (Fig. 7C). The

slow waves were smaller with the latter drug, suggesting that inhibition along the sympathetic route was more complete with SC 1950. In the same subject, 1.0 mg. of SC 1950 given intravenously failed to influence the spontaneous vasomotor activity in any way. Thus, if one compared the drugs on a similar dosage basis, CCK 179 would be considered more effective.

The effects of CCK 179 on sweating were studied on 5 normal subjects and 5 patients with hypertension. The electrodes were placed on the second and third fingers of the left hand. Sanborn EKG electrode paste was applied between the electrode and the skin. The skin resistance and psychogalvanic reflex to inspiration and startle were studied at 10-minute intervals for 40 minutes before and after the intramuscular injection of 1.0 mg. of CCK 179. An average decrease in skin resistance of 3000 ohms and absence of

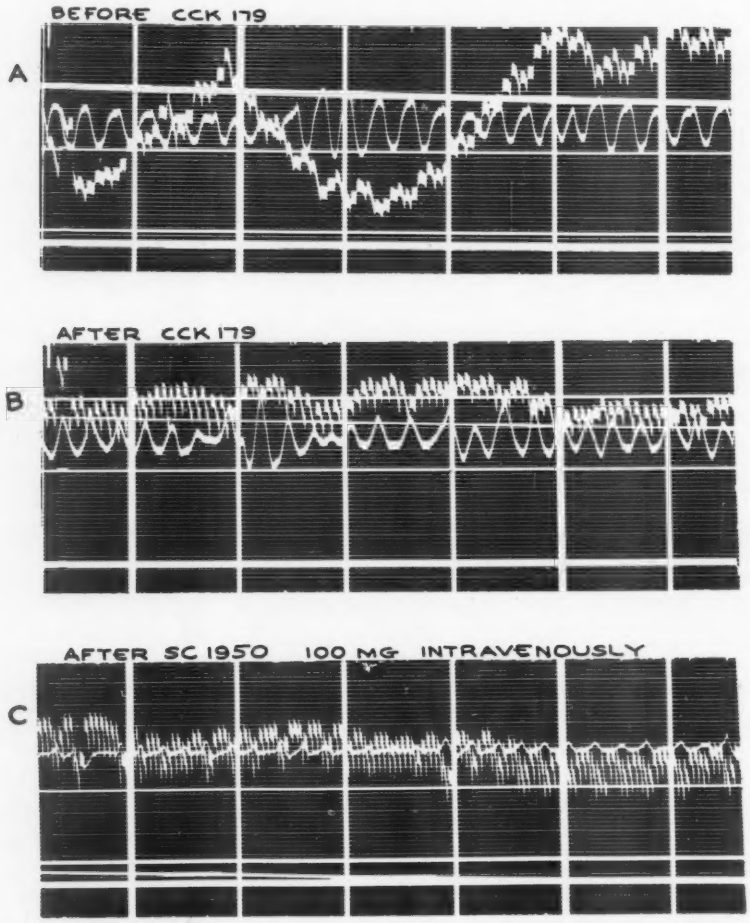

FIG. 7.—Comparison of effects of 1 mg. of CCK 179 given intravenously with 100 mg. of SC 1950 given intravenously on the spontaneous waves of the plethysmogram. There is a reduction in the size of the slow wave forms indicating a depression of the sympathetic nervous system with both drugs.

the psychogalvanic reflex occurred in all 30 or 40 minutes after the drug. This finding, along with blocking of the induced vasomotor reflexes, suggests blocking of the sympathetic pathways innervating the sweat glands of the hand.

The *local cutaneous effects* were tested by injecting 0.1 cc. of 1:10,000 epinephrin into the skin of 5 normal subjects in dilute dosage with the production of a large blanched area. Into this area 0.5 cc. of histamine 1:1000, 0.5 cc. of priscoline 25 mg. per cc., 0.5 cc. CCK 179 0.3 mg. per cc., and normal saline solution were introduced. A definite erythema and wheal occurred with histamine and priscoline, suggesting a local vasodilating action capable of overcoming vasoconstriction produced by previously injected epinephrin. A slowly developing but definite erythema occurred with CCK 179. In the control, which received normal saline solution, no erythema and no wheal occurred. Thus, it is felt that CCK 179 has properties suggesting a local mild adrenolytic action. Similar findings were noted when 0.1 cc. levoarterenol bitartrate 1:1000 was used for the original intracutaneous injection. Others have pointed out a definite adrenolytic and noradrenolytic action of CCK 179 on the arterial pressure of man[9,12] and an antiangiotonin effect on the arterial pressure of animals[3].

Discussion. CCK 179 constantly produced a hypotensive effect after intravenous injection of 1 mg. with the subject supine and occasionally had a similar effect after 3.0 mg. of the drug were given orally if the subject remained erect for the duration of the test. The mode of action of CCK 179 seems in part to be that of a sympathetic nervous system depressant acting centrally, at the ganglion, or peripherally. This is shown by the decreased peripheral resistance, accompanied by an inhibition of both the induced and spontaneous vasomotor activity of the digits, inhibition of acral sweating, and a decrease in the cold pressor response after the administration of the drug.

Other actions are recorded in the literature. For example, its anti-norepinephrin and anti-epinephrin action[9,12] may play a significant role in lowering the arterial pressure in patients with certain types of hypertension. Approximately one-half of the patients with hypertension in this series had relief of hypertensive headaches when taking CCK 179. The mechanism of action of the relief of headache in certain of these patients may be based on a decreased cerebral arterial resistance as has been reported elsewhere[10], or to a direct central action as shown by the nausea, sedative effect, and slowing of the cardiac rate seen in these patients[1]. A divergence of opinion exists as to the cardiac output[6,15]. It was measured by Werko[15] on 5 patients with arterial hypertension following a single intravenous dose of DHO. He found that the cardiac output fell slightly. One of his patients, a 44-year old female, after 0.5 mg. of DHO, however, showed an increase in cardiac output from 8.95 to 9.3 liters per minute. This occurred 28 minutes after injection. Because of the apparent depressor effect of this drug when taken orally, in certain patients with hypertension, further careful investigation over long periods of time with various dosage schedules on patients with various types of hypertension is clearly indicated. These studies showing an acute hypotensive effect of the drug suggest that it should be tried over long periods of time to determine whether or not the hypotensive effect can be maintained.

Summary. CCK 179 is a depressor drug capable of at least transient lowering of the arterial pressure after oral or intravenous administration of a single adequate dose, particularly when the blood pressure is recorded with the subject in the erect position. The depressor effect is variable and appears to be most marked when there is a significant neurogenic aspect to the hypertension. The duration of the effect when repeated doses of adequate size are employed is not known. The drug has a central sedative action and depresses slightly the cold pressor response. The induced and spontaneous vasomotor changes of the digit and reflex sweating are significantly inhibited, indicating sympathetic nervous system depression. The amelioration of hypertensive headaches is not uncommon.

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THE EFFECT OF PARA-AMINOSALICYLIC ACID (PAS) ON THE DEVELOPMENT OF RESISTANCE OF TUBERCLE BACILLI TO STREPTOMYCIN.*

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THE effectiveness of streptomycin and dihydrostreptomycin in the treatment of tuberculosis has been well demonstrated. The chief obstacle to their use has been the development of bacterial resistance. Most observers[1,2,6] report the development of resistance in over half of the patients treated with streptomycin alone after a treatment period of from 90 to 120 days.

Graessle and Pietrowski[3] report that the addition of para-aminosalicylic acid (PAS) to streptomycin markedly delays the emergence of resistance of the tubercle bacillus to streptomycin in vitro.

Karlson and associates[4], treated 14 patients with combinations of streptomycin and PAS or promin and PAS. One patient developed streptomycin resistant tubercle bacilli at the end of 3 months. At the end of 6 months of treatment 3 more showed resistant strains.

A controlled investigation was conducted by the British Medical Research Council[5] in which patients receiving daily streptomycin only were compared with a group receiving daily streptomycin and PAS for a period of 3 months. This study demonstrated that 89% of the combined therapy patients producing positive cultures had sensitive strains at the end of 6 months compared to 21% of the streptomycin treated patients.

The present report concerns the study of the development of bacterial resistance under three treatment regimens: 1) Dihydrostreptomycin alone, 2) Dihydrostreptomycin and PAS, and 3) Streptomycin and PAS.

Method of Study. Patients were selected who had far-advanced pulmonary tuberculosis in order to obtain continued production of positive cultures as readily as possible. The number of patients in each group was comparable. There were 24 patients who received dihydrostreptomycin, 25 dihydrostreptomycin and PAS, and 25 streptomycin and PAS. Streptomycin or dihydrostreptomycin was given in 1 gm. daily dosage intramuscularly for 13 weeks. PAS was given by mouth in 4 equal doses totalling 10.0 gm. a day. The drug was neutralized by the addition of sodium bicarbonate, 6 parts to 10 parts of PAS. Cultures were made from sputum or gastric contents on Petragnani's egg yolk medium and forwarded to Dr. Guy Youman's laboratory at Northwestern University, Chicago, Illinois, for resistance study both to streptomycin and PAS. Cultures were obtained during the pre-treatment observa-

* This investigation was supported (in part) by a research grant from the National Institute of Health, Public Health Service.

tion week and at the 4th, 6th, 8th, 10th, 12th, 14th, 18th, 22nd, and 27th week from the beginning of treatment. All were made in duplicate on separate days during each observation week. Organisms were considered sensitive when they were found sensitive to 10 mcg. per cc. or less, partially resistant when reported as resistant to 10 mcg. per cc. but sensitive to 100 mcg. per cc., and resistant when growth occurred in a concentration above 100 mcg. per cc. Resistance to PAS was reported in concentrations of 0.1 mg. per 100 cc., 1 mg. per 100 cc. and 10 mg. per 100 cc.

1), resistance appeared in the fourth week in 24% of the patients, and showed a steady increase to 58% at the end of therapy, following which it levelled off throughout the observation period to approximately 45%.

In those patients receiving dihydrostreptomycin and PAS (Fig. 2), resistance appeared in the fourth week in 8% of the patients. At the end of therapy, only 4% were resistant, and at

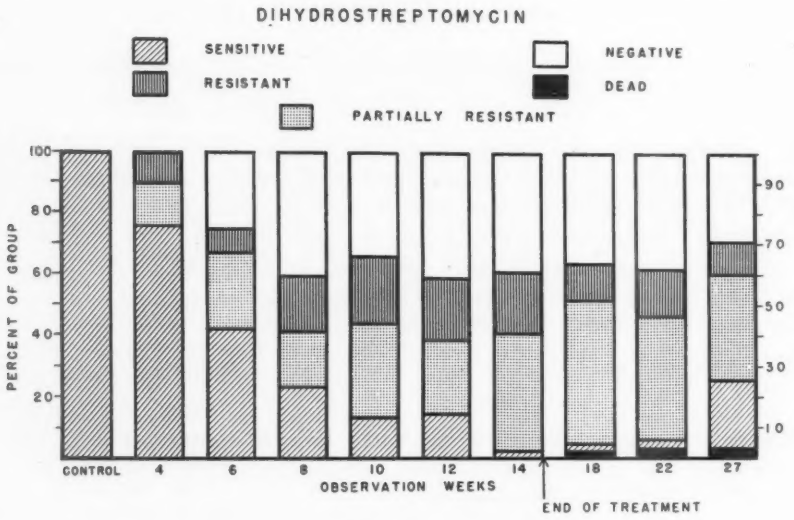

FIG. 1

Results. All pre-treatment cultures were returned as sensitive except in 8 patients. Reports of the duplicate cultures in these instances showed both sensitive and partly resistant organisms. None of these patients had received previous streptomycin or dihydrostreptomycin therapy as far as could be determined. Observations on subsequent cultures of all 8 showed them to have sensitive organisms. None of the cultures showed organisms resistant to PAS at any time during the course of the study.

1. DEVELOPMENT OF RESISTANCE. In the dihydrostreptomycin group (Fig.

the end of the observation period, 6% were resistant, and those were in the partially resistant group.

In those patients treated with streptomycin and PAS (Fig. 3), resistance appeared in the fourth week in 12% of the patients, and at the end of therapy, 16% showed resistant cultures. At the end of the observation period, 26% were resistant.

2. MAINTENANCE OF SENSITIVITY. In the dihydrostreptomycin group (Fig. 1) there was a rapid decrease in the percentage of sensitive cultures obtained, from 100% in the pre-treatment week, to 4% at the end of drug

therapy. At the end of the observation period (three months after cessation of therapy), it rose to 22%.

In the dihydrostreptomycin – PAS group (Fig. 2), there was a steep decrease in the percentage of sensitive cultures from 100% to 42% at the end of 10 weeks, 44% at the end of 14 weeks, and 44% at the end of the study.

In the streptomycin–PAS group (Fig. 3), there was a steep decline in the percentage of sensitive cultures from 100% to 36% at the end of 10 weeks, and rising to 46% at the end of the treatment period, and decreasing to 16% at the end of the observation period.

3. Conversions – Development of Negativity. In the dihydrostreptomycin group (Fig. 1) there were no conversions at the end of 4 weeks, 38% at the end of 14 weeks and 28% at the end of 27 weeks.

In the dihydrostreptomycin – PAS group (Fig. 2) there were 4% conversions at the end of 4 weeks, 48% at the end of 14 weeks and 44% at the end of 27 weeks.

In the streptomycin–PAS group (Fig. 3) there were 16% conversions at the end of 4 weeks, 38% at the end of 14 weeks and 53% at the end of 27 weeks.

Discussion. It is evident that the addition of PAS to streptomycin or dihydrostreptomycin therapy results in a marked diminution in the number of resistant cultures at each period throughout the study. This was particularly evident in the dihydrostreptomycin–PAS treated patients. In this group only 6% were partially resistant at the end of observation and all remaining positive cultures were sensitive. In the streptomycin–PAS group there was a marked delay in the emergence of resistance. However, at the end of the observation period 26% of the cultures showed resistance, a much higher number than the dihydrostreptomycin–PAS group, but much lower than the dihydrostreptomycin patients.

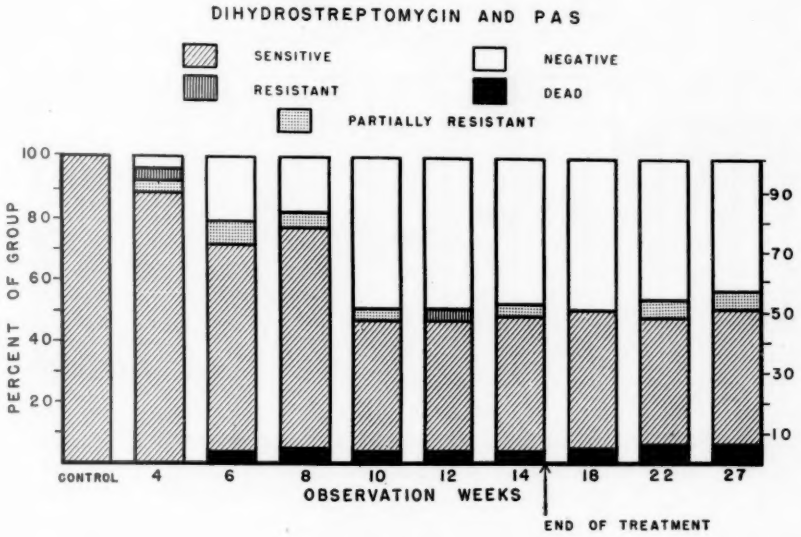

Fig. 2

At this time we have no adequate explanation for the discrepancy in the 2 groups on combined therapy.

The dihydrostreptomycin – PAS group showed the greatest maintenance of sensitivity in each observation period. The streptomycin–PAS group showed a much greater maintenance of sensitivity than the dihydrostreptomycin group during the first 18 weeks of observation following which there was a marked decrease in the number of sensitive cultures. At the end of 27 weeks there was little difference between the dihydrostreptomycin – PAS and the streptomycin–PAS groups in respect to the maintenance of sensitivity.

Both of the combined treatment groups showed a marked advantage in the number of conversions at each period compared with the group which received dihydrostreptomycin alone.

Conclusions. 1. The addition of PAS to streptomycin or dihydrostreptomycin markedly delays the emergence of resistant organisms.

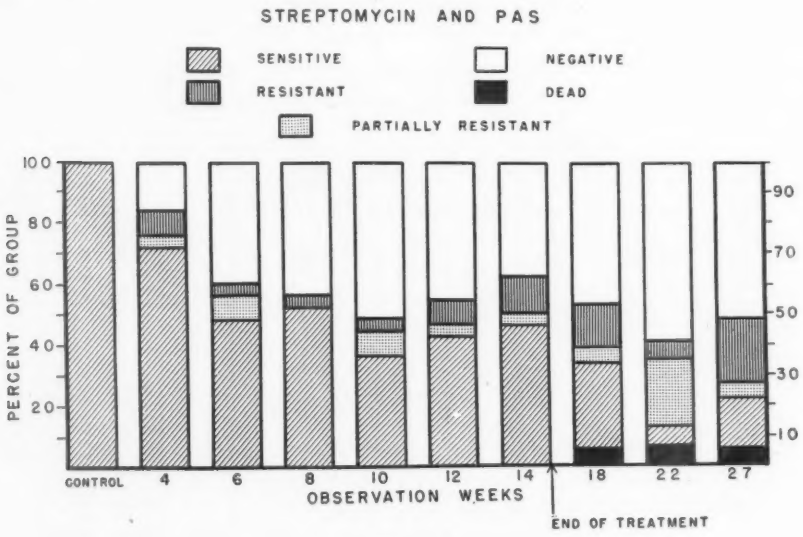

FIG. 3

2. Combined therapy for a period of 3 months results in decrease in resistant organisms during this interval and for 3 months thereafter.

3. The addition of PAS to streptomycin or dihydrostreptomycin increases the number of sputum conversions both during the treatment period and the subsequent 3 months.

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ANTHRAX MENINGITIS:

REVIEW OF LITERATURE AND REPORT OF TWO CASES WITH AUTOPSIES

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In recent years infections with the anthrax bacillus have become increasingly rare, and the occurrence of meningitis as a complication is even rarer. The observation of 2 cases of anthrax leptomeningitis at the Boston City Hospital during the past 5 years has prompted the present report, which is an attempt to review the literature briefly and to report the details of these 2 cases, with an additional note on therapy. Although anthrax meningitis is rare, it is worth pointing out the salient features of the condition since some cases may now be curable.

Literature. The first reported cases were those of Wagner[83] who in 1874 described the pathological changes in anthrax meningitis. Very little of importance has since been added to his original descriptions. Following his first mention of 3 cases of hemorrhagic meningitis, there have been isolated case reports, most of them in the German literature. In 1881 Greenfield[35] reported 3 cases of anthrax meningitis following wool-sorter's disease in England, and subsequently single case summaries have appeared sporadically. Bruce and Shennan[6] in 1910 were able to find in the literature only 26 verified instances of meningitis due to *Bacillus anthracis*, to which they added 1 of their own. In 1920 House[45] collected 45 cases in the literature and reported 3 of his cases with detailed descriptions of the gross and microscopic pathological changes. Since 1920 there has been no general review of the world literature, and it seemed pertinent to the present report to summarize the available data.

There are now described some 95 cases of anthrax meningitis, but of these only 70 are reported in sufficient detail to allow comprehensive analysis.* Some of these data are summarized in Tables I and II.

Bacteriology. *B. anthracis* was obtained from cultures of the cerebrospinal fluid either during life or at autopsy in all reported cases. In 1 instance a culture was negative for the organism in the presence of meningeal signs clinically and was later reported as positive at autopsy[46]. The presence of a positive blood culture has not been a consistent or helpful finding, but this is not too surprising since the septicemic stage is reached relatively late in the course of the infection, and by this time, if meningitis is to develop, other manifestations have generally appeared. Parenthetically, it might be added that septicemia is not universally a grave sign, for Cowdery[13]

* These 70 cases are contained in the following references: 2 ,3, 5-8, 10, 12, 14-19, 21, 23, 25-30, 34, 35, 37, 38, 39, 41, 42, 45-49, 51, 53-56, 58, 59, 61-67, 69, 71, 72, 73, 76-79, 81-85, 87, 91.

has shown that anthrax bacillemia is not uncommon late in the course of uncomplicated cutaneous lesions from which the patient recovers. As noted below, there have been only 8 instances in which a primary focus for the meningitis could not be demonstrated, and thus the most important bacteriological help has been obtained by making the diagnosis early from stained smears or cultures of the primary focus.

died of hemorrhagic anthrax meningitis which was presumed to have been acquired from the blood stream of the mother, who was infected with the anthrax bacillus[53].

No known primary focus was found in 8 cases after careful search at postmortem examination[10]. From each of these 8 patients an adequate history, physical examination, and laboratory data had been obtained and in no case

TABLE 1.—PRIMARY FOCUS FOR ANTHRAX MENINGITIS IN 70 CASES

Focus	*No. of Cases*	*%*
Skin	37	52.8
Lungs	16	22.9
Intestines	6	8.6
Skin & Lungs	1	1.4
Skin & Intestines	1	1.4
Maternal Septicemia	1	1.4
None Found	8	11.5
	70	100

TABLE 2.—SUMMARY OF CHARACTERISTICS OF ANTHRAX MENINGITIS IN 70 REPORTED CASES

Spinal fluid culture +	100%
Bacteremia	70%
Sex ratio	Males, 3; Females, 1
Age range	Newborn to 71 years
Meningeal signs +	100%
Leukocyte counts	10,000 to 80,000
Average duration of illness	2–4 days
Duration if meningeal signs early	24–36 hours
Hemorrhagic meningitis +	100%
Cortical hemorrhages +	50%

Portal of Entry. The primary focus for the meningitis could be ascribed to a cutaneous source in 37 of the 70 cases, and of this group the face and neck were the most commonly encountered areas. Meningitis secondary to pulmonary infection was seen in 16 cases, and here also one instance was noted with infection of both the skin and the lungs[72]. An intestinal site was found in only 6 cases, with one other patient having involvement of both the skin and gut[83]. One newborn infant

could any clues be gleaned as to the possible source of the infection. This type is frequently referred to in the literature as "primary anthrax meningitis."

Although from these data it is obvious that a primary cutaneous focus is the most commonly associated lesion, no statistically valid relationship can be worked out between the focus of the infection and infection of the meninges. It is interesting that, although virtually all untreated patients with the

intestinal and pulmonary forms of anthrax die[88], only 20% of the untreated cutaneous lesions proved fatal[22]; furthermore, the skin is still the major focus of infection for the meninges, but it is not out of the realm of possibility that the pulmonary form has a higher incidence but is more often unrecognized.

Among the 45 cases reported by House[45] there are only 7 in which meningitis followed either an intestinal or a pulmonary form of the disease; however, details concerning this aspect are given in only 29 of the 45 cases. Among these 7 cases only one brain showed cerebral hemorrhages at autopsy. There is no good correlation between the character of the local skin lesion and the severity of the meningitis. By and large, however, if the cutaneous lesion is specifically characterized by considerable edema, congestion, and swelling, and if a typical local pustule does *not* appear, the disease seems more likely to become serious at an earlier stage and thus more apt to be fatal[6], although many exceptions to this are noted in the literature[30]. A significant clinical point in relation to the primary focus is that cultures of the lesions if obtained early enough are almost always positive for the anthrax bacilli; this necessitates, of course, a high index of clinical suspicion that the lesion is not just an ordinary carbuncle.

Pathogenesis. The routes by which the organisms reach the central nervous system have long been controversial and the evidence is still inconclusive. Two possible routes have been considered, namely, lymphogenous and hematogenous. Fulci[29], Risel[66], Herzog[41], and Bruce and Shennan[6] have cited examples of probable lymphatic spread. The occasional presence of hemorrhagic lymph nodes in areas adjacent to primary lesions, be they in the skin, lung, or gut, strongly suggests some spread of the infection by this means[9]. Furthermore, the recovery of the bacilli from the nodes is even better proof[13]. On the other hand, the high incidence of septicemia (70%) cannot be overlooked, and the great propensity of the organisms to affect the blood vessels so markedly is well established. Without postulating some sort of blood-borne infection, it would be difficult indeed to explain the spread of the anthrax bacilli from the intestine or the lung to the meninges. The frequent presence of an intense diffuse arteritis cannot be adequately explained except by implicating some type of an intravascular spread of the infection. It would seem probable, therefore, that the spread of the infection from the primary focus to the meninges occurs by either of these routes.

Young *et al.*[90] performed extensive experiments on various laboratory animals which had been exposed to aerosols of anthrax spores; they concluded that although a fatal septicemia might result from such an exposure, the disease process was definitely not characterized by pneumonia or other specifically localized lesions. These results are difficult to evaluate in terms of human infections, but they do suggest a possible mechanism of infection for those cases of so-called "primary anthrax meningitis." There is also the work of Cernaianu[11] who showed that the central nervous system *per se* is equally as receptive to the infection as the skin. Such experiments do not, however, further clarify the method of spread of the organism within the human body.

Clinical Features. Although the great majority of the meningitis cases have occurred in young to middle aged males, this is almost certainly due to the increased occupational ex-

posure of this particular group. Of the 8 cases of so-called "primary meningitis" the incidence was greater in the lower age groups, without regard to sex. The age range of the cases in the literature was from the newborn infant to 71 years, with a preponderance in males of 3 to 1 over females.

In every reported case with good clinical documentation the symptoms of meningeal or cerebral irritation preceded death by at least a matter of hours[45]. This accounts for the fact that the death had usually been ascribed to a cerebral lesion of unknown etiology in those instances in which the diagnosis of anthrax meningitis was not made until autopsy. However, typical symptoms of leptomeningitis were the initial complaints in many of the patients. In this group naturally fall the 8 cases of primary meningitis; but in addition there were several patients who had primary foci, with which there either had been no associated symptoms or in which the symptoms of meningitis were too trifling to arouse attention of the patient.

Frequently, there was a sudden onset with malaise, intense headache, dizziness, chilliness or frank chills, myalgia, nausea and vomiting, and general restlessness. The occasional presence of a petechial rash makes the differential diagnosis from meningococcemia important[30]. Delirium often supervened within less than 24 hours; in such cases there was a very rapid progression and convulsions were quite the rule. With the onset of deep coma the convulsions generally ceased and death followed soon afterwards. Gilmour and Campbell[30] reported one instance of a patient who remained fully conscious until 1 hour before death and yet at autopsy showed multiple cerebral hemorrhages. Hitzig[42] has mentioned the only case that developed meningeal irritation at the same time that the primary lesion appeared on the arm. Whereas the temperature usually was very high initially, just prior to death, it tended to drop to abnormally low levels. Leukocytosis was the rule and occasional counts as high as 60,000 to 80,000 have been noted[45] .

Duration of Illness. The average duration of the illness was from 2 to 4 days, with a range of from 1 to 6 days. When the meningeal signs were a prominent part of the early clinical picture, the course was much more fulminating and averaged only 24 to 36 hours.

Incidence. No statistically valid data are available on the exact incidence of meningitis as a complication of anthrax. Shanahan and his associates[73], in their report of 66 cases of cutaneous anthrax at a rug manufacturing company, had 4 patients with meningitis, or about 5%. This proportion would not appear to hold, however, for all cases. Smyth in a U. S. Public Health Service survey found that there were 60 to 80 cases of anthrax annually in the United States and that 95% of these were of the cutaneous variety[74]. He did not mention a single case of meningitis in this group. Wolff and Heimann[89] more recently reviewed the problem of industrial anthrax in the United States and concluded that 98% of the patients had the cutaneous variety; they also did not mention a single case of anthrax meningitis in a group of over 2400 cases studied.

Autopsy Findings. While it is not the purpose of this report to describe in detail the postmortem findings in the reported cases of anthrax meningitis, it is nevertheless worth noting certain conclusions which seem warranted on the basis of those cases in which autopsies were performed and adequate details are recorded. In every instance a hemorrhagic meningitis was

noted as the minimal degree of central nervous system involvement; in roughly a third of the cases the lesions could be described as a meningoencephalomyelitis. Cortical hemorrhages, either gross or microscopic, were present in approximately half of the brains; this agrees well with Szendey's figure of 40% published in 1930[78]. The hemorrhagic aspect of the disease is so striking that it has been repeatedly stressed that extreme care must be taken in differentiating this condition clinically from spontaneous subarachnoid hemorrhage in the early stages. The pathological nature of the primary lesions was typical, whether they were in the skin, lungs, or intestines, and it was frequently possible to culture the anthrax bacilli postmortem as well as to see them on stained smears. The bacilli are likewise commonly seen in the meninges, the subarachnoid spaces, and in the brain substance itself, particularly in connection with the intense arteritis that is so striking.

PROGNOSIS. To date, only 2 patients with proved anthrax meningitis have ever survived. The first case was reported by Czyhlarz[15] in 1919, the diagnosis having been made from a lumbar puncture. This patient received serum therapy and recovered after a long and stormy course. The second patient, reported by Shanahan and his associates[73], was a man who worked in a rug factory, where the initial cutaneous anthrax lesion had been noted; he was started on both antiserum and penicillin therapy, and when the meningeal signs developed in the course of the disease, this therapy was continued, with the addition of intrathecal penicillin. The latter patient gradually improved after a prolonged convalescence.

TREATMENT. Before Koch's report in 1876 on the anthrax bacillus as the etiologic agent in the infection[44], most of the therapy was directed at the local lesion. Following Pasteur's successful vaccination of animals in 1880, it was not long before antisera for humans were developed. In 1903 Sclavo[70] introduced his antiserum which was used extensively. Pijper[60] in 1926 reported on the therapeutic effectiveness of neoarsphenamine with or without antiserum for the treatment of cutaneous anthrax. Lucchesi and Gildersleeve[52] described their experience with the use of combinations of arsenicals and sulfonamides. Many other authors reported on the problem, but Gold[31] wrote the most critical review, concluding that there was little indication that the arsenicals should be used in view of their toxicity and relative ineffectiveness.

Abraham *et al.*[1] in 1941 stated that *B. anthracis* had the same degree of sensitivity to penicillin as the staphylococcus. Following this observation many animal experiments were performed; among them were those of Heilman and Herrell[40] who showed in 1944 that mice infected with the organisms showed a high degree of protection when treated with adequate amounts of penicillin. Barnes[4] wrote that the main problem with penicillin therapy was 1) the production of penicillinase by *B. anthracis*, 2) the persistence of the spores in the tissues and their germination after the levels of penicillin in the blood had fallen and 3) the variation in natural resistance to infection.

Following the introduction of penicillin and after these observations in animals, the agent has been widely used in patients with the cutaneous form of anthrax. Murphy *et al.*[57], Ellingson *et al.*[24], Griffin *et al.*[36], Weinstein and Oliver [86], LaBoccetta[50], Holgate and Holman[43], and others have reported cases of cutaneous anthrax treated successfully with penicillin or

antiserum, or both, in various combinations.

With the advent of the newer antibacterial agents it was only natural that they too would be tried in the treatment of the cutaneous form of the disease[80]. Aureomycin has been used successfully in several cases reported by Gold[32] and by Ruiz-Sanchez[68]. Additional cases were treated with aureomycin, terramycin, and chloramphenicol by Gold and Boger[33]. From their data it would appear that these agents offered some promise in the treatment of the infection.

No specific data on the treatment of anthrax meningitis with antibiotics are available, but it may be assumed that any form of therapy that is efficacious in the treatment of the cutaneous, pulmonary, or intestinal forms of the disease will be efficacious in treating the meningitis, if the agent can penetrate to the appropriate areas.

Case Reports. CASE 1. A 61-year old white male wool-sorter entered the Boston City Hospital on May 5, 1946, in a confused state and unable to give a history. He had been referred here by his physician who had first seen him 5 days previously when he developed a small sore at the angle of the left jaw, which became ulcerated and indurated. The physician noted the lesion and fever, took a culture, and started the patient on penicillin 25,000 units intramuscularly every 3 hours. The culture was later reported positive for *B. anthracis*. By the following day the temperature was normal and it is not known whether or not he received further penicillin between this time and the day of admission here. At 4 A.M. of the day of entry the patient suddenly became ill, having felt essentially well for the 3 previous days. His temperature was 105° F.; shortly afterwards he began to vomit and lapsed into a semicomatose state, with definite signs of meningeal irritation. Because of the progression of symptoms, he was admitted to the hospital.

The patient had been working on Chinese wool, but it is not known whether this or the burlap bags in which it arrived might have been the source of the infection. None of his fellow employees were known to have developed cutaneous anthrax lesions.

PHYSICAL EXAMINATION. At the time of admission the rectal temperature was 103.2° F., pulse 70, respiration 24, and blood pressure 140/90. The patient was a well-developed, well-nourished white male, semi-stuporous, thrashing about the bed and appearing acutely ill. He had gross tremors of all limbs. The skin was hot, dry and pale and no petechiae were observed. At the angle of the left jaw was a 10x10 cm. reddish-purple indurated mass under the skin, covered by a small central eschar. The musculo-skeletal system was normal. A few small left submaxillary nodes were palpable. There was no evidence of old or recent injury to the cranium. The pupils were small, round, regular, and equal, and reacted sluggishly to light; the conjunctivae were injected; the fundi could not be visualized. Both auditory canals and ear drums appeared normal. The throat appeared normal but there was a gross tremor of the tongue. The neck was markedly rigid. There was no venous distention; the trachea was in the midline; the thyroid was not palpable. The chest was symmetrical with equal expansion and slightly increased anteroposterior diameter. The lungs were resonant to percussion, with diffuse rhonchi throughout and occasional moist rales at the right base. The heart was not enlarged; the sounds were muffled, with no murmurs or adventitious sounds noted; the pulse was slow and regular. The abdomen revealed no masses, tenderness, spasm, or palpable organs. Genitalia were normal adult male. All deep tendon reflexes were hyperactive and equal. Marked nuchal rigidity, Kernig and Brudzinski signs, and bilateral ankle clonus were present. The Babinski reflex was thought to be present bilaterally. The sensory system could not be evaluated.

LABORATORY FINDINGS. The blood hemoglobin was 13 gm. per 100 cc., the leukocyte count 22,500 per c.mm. with 90% polymorphonuclears, corrected sedimentation rate 14 mm./hour (Wintrobe), hematocrit 39%, icterus index 7.5. The blood nonprotein nitrogen was 31 mg. per 100 cc., total protein 6.16 gm. per 100 cc. A culture of sputum showed *B. coli, N. catarrhalis,* diphtheroids, and alpha hemolytic streptococcus; the blood culture yielded no growth, but a culture of the facial lesion showed *B. anthracis*. The lumbar puncture showed an initial pressure of 500 mm. of water; the fluid was cloudy, opalescent and pinkish, with a xanthochromic supernatant; it contained 2790 white blood cells with 95% polys. The Pandy was 2+, total protein 211 mg. per 100 cc., the sugar 57 mg. per 100 cc., chlorides 634 mg. per 100

cc. A gram-stained smear of the fluid showed large gram-positive rods in long chains and a culture yielded *B. anthracis.*

COURSE. When the lesion on the neck was punctured for culture, about 5 to 10 cc. of dark sanguineous material exuded. This yielded anthrax bacilli on smears and cultures. Following the initial lumbar puncture, with reduction of the pressure from 500 mm. to 150 mm., the patient became quiet and relaxed. Previously 10 cc. of paraldehyde given intramuscularly had not affected his restlessness. The patient was given 100,000 units of penicillin intrathecally in 10 cc. of normal saline solution; he also received 100,000 units intravenously and was thereafter maintained on 25,000 units intramuscularly every 3 hours. He then again became somewhat agitated and required restraints. Caffeine sodium benzoate, 0.5 gm. intramuscularly every 2 hours, was administered throughout the night. Gradually he became less restless and slumped into a deep coma. The patient then commenced to show more definite focal spastic convulsive movements of the face, left arm, and right thigh. His temperature remained high and rose to 105° F., pulse to 120, respiration to 50 to 60 per minute with Cheyne-Stokes breathing. A lumbar puncture performed at 3:30 A.M. revealed again a pressure of 500 mm. of water and the same type of fluid; another 100,000 units of penicillin were instilled intrathecally. The pulse became gradually weaker; the patient had drenching sweats and remained comatose and showed progression of his focal neurological signs. The lungs remained essentially clear. He quietly expired at 6:45 A.M. on the second hospital day, about 14 hours after entry.

AUTOPSY. (Performed by Drs. Carl Pearson, F. E. Jones and R. D. Adams at the Mallory Institute of Pathology.) The lesion at the angle of the left jaw was noted to be dark, crusted, flattened, about 2 cm. in diameter, with a surrounding 2 cm. of erythema. Grossly the lungs showed fine adhesions at the left apex, with firm, raised, yellow-green nodules in both upper lobes. On section there were seen several large areas of caseous necrosis, with lymphocytes and Langhans giant cells, typical of fibrocaseous tuberculosis. The spleen was enlarged, flabby in consistency, and dark chocolate-red in color, and showed much congestion and many polymorphonuclears on stained smears. There was a large amount of dark red clotted blood in the subarachnoid space but no purulent exudate. Petechial hemorrhages were seen in the superficial layers of the cerebral cortex microscopically. Anthrax bacilli and red blood cells were abundant in the pia and the subarachnoid space. Polymorphonuclear leukocytes and macrophages were found in the cortical substance, and there was some shrinkage and pyknosis of nerve and glia cells suggesting ischemic necrosis. The remainder of the examination was not remarkable. Cultures taken at autopsy were nonspecific except those from the meninges which yielded *B. anthracis.*

CASE 2. A 29-year old unemployed Negress, separated from her husband, was brought by the police ambulance to the Boston City Hospital because of stupor of 12 hours' duration. The history as obtained was grossly inadequate and unreliable, inasmuch as the patient's mother, separated husband, roommates, and a close friend knew little of her recent activities. She was said to have been a chronic alcoholic for at least 2 years, consuming up to 1 quart of wine daily and eating poorly, especially in the last 3 months. Frequent episodes of the "shakes" had occurred, but were never severe enough to require hospitalization. One week prior to admission after being on a drinking spree she developed mild shakes. From that time until entry to the hospital she allegedly ate nothing but an occasional bowl of soup. Three or 4 days later friends saw her walking about, and she appeared well. Two days before entry she was noticed playing with her new pet dog, and she mentioned having a mild headache that day. About 24 hours prior to admission the patient telephoned her mother and complained of an "upset stomach"; 6 hours later she told a friend that she felt dizzy and could not walk, and 12 hours before entry she was found unresponsive in bed. This, however, was not considered with too great alarm in view of her alcoholic habits; but 8 hours later she was sent to the hospital.

The past history is of interest only insofar as the patient, her husband and their 3 children were treated for syphilis in the out-patient department 10 years ago. Her menstrual periods were said to have been irregular for the last 6 months and the patient's mother stated that she might have had a spontaneous abortion 2 months previously, when she had passed some "very large clots."

PHYSICAL EXAMINATION. At the time of admission the temperature was 105° F., pulse 130, respiration 36, blood pressure 120/80. The patient was a well-developed, fairly well-nourished young colored female, who

was comatose, breathing stertorously and irregularly, having frequent generalized convulsions, and appearing acutely ill and almost moribund. The skin was very hot, moist, and showed no evidence of rash, petechiae, or recent or old lesions of any sort. The patient had rigid extremities, with the sacrospinalis and extensor muscles of the legs held in almost constant spasm bilaterally. The spine was often held in opisthotonus. There was no remarkable lymphadenopathy. Moderate peri-orbital edema was present bilaterally, with a strong suggestion of proptosis on the right. Between convulsions the eyes were pulled down and to the right; during convulsions they were down and to the left. The pupils were miotic, regular, and equal and reacted very sluggishly to light; the conjunctivae were clear and the fundi appeared normal. No evidence of sinus infection could be found. The ear drums were slightly thickened bilaterally but the landmarks were clear, with no bulging or injection. Dental hygiene was very poor. The neck showed marked nuchal rigidity but no venous distention; the trachea was in the midline. The breasts were normal adult female. The thorax expanded slightly but symmetrically; there was minimal dulness to percussion at the left base posteriorly, with bronchial breath sounds and medium moist inspiratory rales. No changes in fremitus were elicited. The heart was not enlarged to percussion; the sounds were distant and the rhythm was rapid and regular. No abdominal masses, spasm, tenderness, or palpable organs were noted. The patient was apparently menstruating but the uterus, cervix, and adnexae appeared essentially within normal limits from pelvic examination. There was no cyanosis, clubbing, or peripheral edema.

Neurological examination showed a comatose patient with constant rigidity of the legs except during convulsive seizures which occurred every 15 to 20 minutes. She reacted to painful stimuli by withdrawal; the sensory modalities could not be otherwise evaluated. Deep tendon reflexes appeared equal and active bilaterally. The plantar responses were equivocal. The Kernig and Brudzinski signs were present.

Laboratory Findings. The urine was amber, cloudy, without bile, albumin, or sugar, but showed 3+ acetone and the spun sediment contained 0 to 2 white blood cells per high power field. The blood hemoglobin was 10.8 gm. per 100 cc., hematocrit 42%, icterus index 12, leukocytes 14,400 with 78% adult polymorphonuclear neutrophils, 11% band cells, 1% metamyelocytes, 8% lymphocytes, and 1% basophils. The blood Hinton test was positive. The blood nonprotein nitrogen was 34 mg. per 100 cc. chlorides 86 mEq./L., carbon dioxide combining power 46 vol. per 100 cc. The stool was loose and brown and the benzidine test was negative. The initial blood culture yielded *B. anthracis* but 2 subsequent blood cultures were sterile. The lumbar puncture on entry showed an initial pressure of over 350 mm. of water; the fluid was cloudy, opalescent, with slight xanthochromia; there were 3000 leukocytes of which 82% were neutrophils, and 400 red blood cells. The Pandy was 3+, total protein 400 mg. per 100 cc., sugar 56 mg. per 100 cc., chlorides 608 mg. per 100 cc., colloidal gold 1112223333. The stained smears and a culture of this fluid showed *B. anthracis*. A second lumbar puncture 10 hours later showed an initial pressure of 300 mm. of water; the fluid was cloudy, pinkish-yellow; there were 11,700 white blood cells, of which 90% were neutrophils, and 25,000 red blood cells. The total protein was 1000 mg. per 100 cc. A culture yielded *B. anthracis*. A third lumbar puncture performed 28 hours after entry revealed an initial pressure of 120 mm. of water; the fluid was grossly bloody, and cloudy, and had a xanthochromic supernatant portion. There were 58,000 leukocytes, with 95% neutrophils, and 120,000 red blood cells. The total protein was 1333 mg. per 100 cc. The culture was sterile.

Course. The patient was placed on strict isolation precautions and started on oxygen by nasal catheter. Intravenous fluids were administered and to these was added aureomycin hydrochloride, buffered with sodium glycinate, in a dosage of 1.0 gm. intravenously every 12 hours. Frequent pharyngeal and tracheal suctions were required for the removal of rapidly accumulating secretions. Phenobarbital sodium 0.2 gm. intramuscularly was given to control the frequent generalized convulsions. No response in the temperature or the general clinical status could be detected after the first 2 doses of aureomycin. The convulsions had stopped, however, and the spasticity in the legs disappeared. The deep tendon reflexes remained equal and active bilaterally. At the end of 24 hours no significant improvement was noted. The peri-orbital edema persisted but the proptosis of the right eye waned. The pupils at this time were nonreactive to light. The lung signs remained as before. The patient continued in a comatose state, developed increasing respiratory distress associ-

ated with profuse bronchial secretions, and then suddenly became apneic. Despite artificial respiration, tracheal suction, and intracardiac stimulants, she expired approximately 30 hours after entering the hospital.

BACTERIOLOGICAL FINDINGS. (Carried out with the collaboration of Miss Marion E. Lamb and Miss A. Kathleen Daly of the Mallory Institute of Pathology). The initial suspicion of anthrax came when large rods in long chains were seen by the house physician in the unstained cerebrospinal fluid in the counting chamber. On gram-stained smear these organisms were abundant, had definite capsules and usually flat ends, a few being ovoid. No spore forms were noted. The organisms grew well on all media, aerobically and in a candle jar. The colonies were rough, grayish, opaque, with wrinkled surfaces and irregular serrated edges. Smears of the growth in broth confirmed the presence of the capsules and in a hanging-drop preparation the organisms were shown to be non-motile. The broth cultures were characterized by a puff-ball appearance at the bottom of the tube; this was also observed in the initial blood culture flask. The growth on routine media of the initial *unspun* spinal fluid was abundant. The second culture of *unspun* spinal fluid, obtained 7 hours after a single dose of 1 gm. of aureomycin intravenously, showed a considerably reduced number of organisms; some bacilli were also seen on smears to be intracellular for the first time. The third spinal fluid culture, of which a *spun* sediment was observed, showed a very rare organism on stained smear and yielded no growth on any of the plates or in the broth. The patient had received 3 gm. of aureomycin intravenously prior to obtaining the last spinal fluid for culture.

The organism was checked for its biochemical properties and was found to coagulate milk, reduce nitrates, hydrolyze starch, and to ferment glucose, sucrose, maltose, and fructose with the production of acid.

Animal studies were performed to verify the pathogenicity of the bacillus. From a 24-hour fresh broth culture of the initial spinal fluid, 0.1 cc. was inoculated intraperitoneally into a healthy white mouse. The animal died within 6½ hours and at autopsy showed *B. anthracis* in the heart's blood culture. Using a similar culture, 0.5 cc. was injected subcutaneously into the thigh of a guinea pig; this animal died in 24 hours and at autopsy had a gelatinous exudate with hemorrhage at the inoculation site. *B. anthracis* was recovered from the liver, heart's blood, and from the spleen, which was typically dark red, congested, and considerably enlarged.

Antibiotic sensitivity studies of the organism were carried out to evaluate the responsiveness to the commonly used agents. Preliminary screening by the disc method showed the bacillus to be inhibited only slightly by penicillin, moderately by streptomycin and chloramphenicol, and markedly by aureomycin and terramycin. More definitive sensitivity determinations by the two-fold dilution method in broth, with subsequent culture on blood agar plates, showed the organism to be completely inhibited by a concentration of 0.8 to 1.6 μgm. of aureomycin hydrochloride per cc.

EPIDEMIOLOGY. A thorough investigation of the case was made through the joint efforts of Dr. Laurence Rainsford of the Massachusetts Division of Communicable Diseases, Dr. Robert MacCready of the State Department of Public Health, and Mr. Dover Roth, a fourth year Harvard Medical School student. A careful study and search of the home environment revealed no positive source of the infection. Cultures were made from the dog's hairs, dog biscuits, a hair brush, a powder puff, and some raw wool to which the patient had been exposed. All were negative for anthrax bacilli. Neither could any personal contact for the infection be established.

AUTOPSY. (Performed by Drs. Herbert Goodman, E. Lang, and R. D. Adams of the Mallory Institute of Pathology). At postmortem examination no skin lesions could be found. There was marked peri-orbital edema bilaterally with chemosis and some yellowish discoloration of the bulbar conjunctivae. The left chest was filled with 1500 cc. of cloudy yellow fluid. The lungs were moderately expanded and without adhesions. The lower portion of the left upper lobe was firm, darker, and noncrepitant, and appeared mucoid on cut surface. Microscopic sections showed marked fibrinous exudate in all alveolar spaces; numerous pigment-laden macrophages were present. No organisms of any sort could be found in the lung tissues. The bronchioles of the left upper lobe were filled with polymorphonuclear leukocytes and gave a suggestion of early abscess formation in some areas. The remainder of the left lung, the right lung, and the upper trachea and larynx were essentially within normal limits. The heart showed a slight increase in interstitial lymphocytes in the myocardium, with a few focal collections of polymorphonuclear leukocytes surrounding the muscle

fibers, showing early necrosis and altered staining. The spleen grossly was soft, dark red, and mushy in consistency, and the gastrointestinal tract was completely negative. There was evidence of chronic pelvic inflammatory disease and bilateral tubovarian masses were seen.

The skull was not remarkable and the dura mater was normal. The leptomeninges were slightly thickened and opaque over the optic chiasm, interpeduncular fossa, and cisterna magna. The cerebral gyri were flattened and the sulci were obliterated. There was very little cerebrospinal fluid present, and what was seen was clear, yellow, and not purulent. Both cerebral hemispheres were swollen, especially the right frontal lobe, which was considerably more prominent than the left. Aspiration of the bulging mass in this lobe yielded a sanguineous fluid with small bits of necrotic tissue. No subarachnoid hemorrhage was noted. The spinal cord, the sinuses and the middle ears were normal. Microscopic sections showed numerous petechial hemorrhages in the cerebral cortex, anthrax bacilli and red blood cells scattered throughout the cortical tissues, a large abscess in the right frontal lobe filled with a hematoma, and considerable necrosis of vessel walls.

Postmortem cultures yielded *B. anthracis* from the right frontal hematoma and the base of the brain only. The heart's blood, liver, spleen, and lung cultures were negative for anthrax bacilli.

Comment. Several points in these 2 cases are worthy of mention. The first patient was an elderly white male with a known occupational exposure to the infection. He had been seen early in his illness by a competent physician, who prescribed what he considered to be adequate therapy for the treatment of the local anthrax lesion. At the present time the physician would probably have used much larger doses of penicillin, but in 1946 the antibiotic was expensive and difficult to obtain, and its value in this disease was not well established. Bacteremia was not demonstrated in this case, in spite of severe meningeal signs and evidence of overwhelming infection, but this may have been related to the previous therapy with penicillin and to the already well-localized primary lesion. However, contrary to the general rule that a well localized lesion, and particularly a treated one, less often results in complications, this patient progressed to a fulminating meningitis and death in less than 24 hours after the onset of the cerebral signs and symptoms. One can only speculate that larger doses of penicillin or another antibiotic used at the outset or even after recognition of the meningitis would have altered the terminal course. It is likely, however, that had the *initial* lesion been treated, as now recommended, with larger doses of penicillin or with 1 of the newer drugs, the outcome might have been altered. This case emphasizes well the need for careful observation of all patients with anthrax of any form, in order to be alerted at the earliest possible moment of the onset of a complication.

The second patient had neither an occupational exposure nor a known environmental one for her infection, and no focus for her meningitis was discovered at autopsy. It would be tenuous to assume that the pneumonic process in the left upper lobe of the lung was anthrax in origin, in view of the complete lack of either pre- or post-mortem bacteriological confirmation and the atypical pathological appearance. She must, therefore, be classified with the previously described 8 cases of "primary anthrax meningitis." From the nature of the basic pathological process in anthrax meningitis, it is not to be expected that the therapy of this type of case would be very successful. However, an opportunity was afforded to observe the effects of therapy on the anthrax bacilli *in vivo*. In this patient, essentially a "bacteriological cure" had been achieved. The clearing of the cerebrospinal fluid of viable organisms after a total dosage of only 3 gm. of

aureomycin intravenously is striking evidence of the effect of the antibiotic upon the organisms. Likewise the blood cultures had become sterile under therapy. This effect was to be anticipated from the previously observed sensitivity of the anthrax bacillus and the closely related species *Bacillus cereus* to the wide-spectrum antibiotics. Gold and Boger[33] have successfully treated several patients with cutaneous anthrax with each of these agents, that is, aureomycin, terramycin, and chloramphenicol, and it was because of their observations that the second patient received aureomycin therapy. *B. cereus* No. 5 is a standard laboratory strain which is used as a test organism in determining the sensitivity of microorganisms to aureomycin[20], and because of its very close biological relationship to *B. anthracis*, one could have anticipated that the anthrax bacilli would be very sensitive to that agent.

Summary. The literature relating to 95 previously reported cases of anthrax meningitis is reviewed and summarized.

Two cases of leptomeningitis due to the *Bacillus anthracis* are presented and their outstanding clinical and bacteriological characteristics are described. In the first case the meningitis followed a cutaneous anthrax lesion; the second case must be considered as another instance of "primary anthrax meningitis."

From the data on the sensitivity of the *B. anthracis* to various antibiotics, it is suggested that aureomycin and terramycin should be effective in the treatment of anthrax meningitis. The first patient in the report was treated with penicillin and the second with aureomycin. In the latter a "bacteriological cure" was almost achieved, although the patient died of severe brain damage associated with the extensive pathology incident to the disease.

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A CLINICAL TRIAL OF PRODIGIOSIN IN DISSEMINATED COCCIDIOIDOMYCOSIS*

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Disseminated coccidioidomycosis has proved resistant to many forms of therapy including the commonly used antibiotics. The prognosis is poor, particularly in non-Caucasians. The purpose of this preliminary report is to present clinical data on a new antibiotic which appears to influence the course of the disease favorably and may be a useful therapeutic agent against disseminated coccidioidomycosis.

Lack[1] found that the purple dye prodigiosin† would inhibit the growth of *Coccidioides immitis* in vitro and[2] that it was non-toxic to animals in amounts that were therapeutically effective in animals infected by intraperitoneal inoculation. The treated animals survived their infection and were sacrificed. The dye was found to be localized in the healed granulomatous lesions, particularly in the lungs.

Because of the susceptibility of Negroes and the fact that in them a disseminated infection is usually fatal, they were selected for study as frequently as possible. Over a period of 4 years, 14 patients were given prodigiosin. Of these, 5 were moribund when therapy was instituted and were treated primarily in an effort to find a non-sclerosing intravenous method of administration.

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The Prodigiosin used for this study was furnished in part from Long Beach Veterans Administration Hospital and in part from the Commercial Solvents Corporation, Terra Haute, Indiana.

Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

† Prodigiosin is a purple tripyrrole methane which may be extracted from cultures of Serratia marcessans (*Bacillus prodigiosus*) with organic solvents including propylene glycol. It is not soluble in water. The method of recovery and purification is to be published by Lack *et al.*[3], and the spectrum of its activity against fungi and certain bacteria by Lack *et al.*[4].

Primary coccidioidomycosis has a favorable prognosis and such cases were excluded by the following criteria indicative of dissemination: 1) Rising titers of the complement fixation test performed in the laboratory of Doctor C. E. Smith[5]; 2) Elevation of the erythrocyte sedimentation rate and elevation of the white cell count above 12,000; 3) Fever persisting over 2 months; 4) "Metastatic" involvement; 5) Toxicity.

Prior to the institution of therapy, the status of liver and renal function was evaluated by the use of laboratory procedures commonly available. These included prothrombin time, thymol turbidity, cephalin flocculation, blood urea nitrogen, complete blood count, urinalysis, erythrocyte sedimentation rate, bleeding and clotting times and pertinent laboratory work for other conditions that might be present. During the course of therapy, a complete blood count, urinalysis and erythrocyte sedimentation rate were done weekly. Liver function studies and blood urea nitrogen determinations were done biweekly. Complement fixation tests, sent to the laboratory of Doctor C. E. Smith were done at 4 or 6 week intervals. The complement fixation and the erythrocyte sedimentation rate were found to be particularly helpful in the clinical evaluation of patients.

Method of Administration of Prodigiosin: Initially the drug was administered locally; the abscesses being infiltrated with it. This caused a local inflammatory reaction which was apparently due to the irritant action of the drug and the reaction upon the abscess. Local infiltration subcutaneously in animals produced an inflammatory reaction also but not to the same extent. When it became apparent that there was no other toxic manifestation and that the previously positive cultures became negative, parenteral therapy was begun, using 1 mg. intramuscularly. A water soluble preparation was employed which had been prepared by the addition of glutamic acid to one of the pyrrole rings of the dye. Intramuscular therapy was gradually increased to a dose of 30 mg. with no signs of toxicity other than local pain for 10 minutes and tenderness lasting about 24 hours. However, the supply of the water soluble prodigiosin was soon exhausted and further preparations could not be obtained. A suitable intravenous preparation was next sought. For intravenous therapy, the dye was dissolved in propylene glycol and administered in gradually increasing doses to a total of 25 mg./day in a single dose. An intravenous dose of 10 mg. given rapidly was occasionally associated with dizziness but this did not occur when the drug was given slowly. Examination of the blood and urine and liver function tests revealed no changes attributable to the use of the drug, the abnormalities present being due to the disease process.

The dye precipitates in the following solutions: procaine, Ringers M/6 sodium lactate, normal saline, protein hydrolysates and in blood serum. This may be the contributory factor in the local venous sclerosis that occurred with such regularity that prolonged courses of medication were precluded. Such precautionary measures as the injection of the material into the tubing of a running venoclysis of 5% glucose in water did not prevent occlusion of veins. For the past 9 months the drug has been tried orally because of the limitations of the intravenous and intramuscular preparations. Blood levels following administration by the oral route have not been obtainable. None has been recovered in the feces of animals in proportionate doses.

Case Reports. CASE 1. A 24-year-old Negro was admitted to Wadsworth General Hospital August 26, 1946, because of multiple subcutaneous abscesses and persistent fever. He was severely ill and emaciated.

Laboratory examination: Red cell count 4,200,000 per c.mm.; white blood cell count 12,100 per c.mm. with 78% polymorphonuclears; sedimentation rate 29 mm. per hour. Coccidioidin skin test was positive in 1:10 dilution. Roentgen-ray studies revealed widening of the hilus and multiple lytic bone defects. Complement fixation for *Coccidioides immitis* was positive in a dilution of 1:64. Cultures from the abscesses grew *C. immitis.*

Course. With supportive treatment alone, he became worse. One of us, (A.R.L.), while visiting Wadsworth General Hospital, was shown the patient and offered to furnish prodigiosin for clinical evaluation. Because of the gravity of the prognosis and in the absence of specific therapy, it was agreed to give it a trial.

The initial therapy was limited to infiltration of the abscesses and consisted of 5 mg. of the water soluble preparation in 10 cc. normal saline, and later 10 mg. in 5 cc. Such treatment was instituted in December, 1946, and continued until the end of May, 1947, by which time a total of 45 mg. had been injected. Injections were usually followed by local inflammatory reaction and occasionally by mild systemic signs of aching, lassitude and fever. The abscesses localized, drained spontaneously and healed in a quarter of the time expected from untreated cases.

On May 5, 1947, intramuscular therapy was instituted beginning with 2 mg. of the water soluble preparation and gradually increasing this until 30 mg. were given in a single injection, all without signs of toxicity. A total of 175 mg. were given intramuscularly by the end of June, 1947. He showed marked improvement clinically and his temperature and erythrocyte sedimentation rate fell almost to normal. He requested and was granted a furlough. On return to the hospital, he showed signs of a new abscess and shortly thereafter of reactivation of an old one. His condition rapidly became serious.

Due to the very small amount of drug available at that time, he was given only 5 mg. locally for a month into one of the abscesses which responded as before along with moderate clinical improvement. From August to November, 1947, he received no specific medication and by November he had begun to fail rapidly with the appearance of numerous abscesses.

Ninety-two milligrams of the drug were made available to us in December and on December 12th a course of intravenous therapy was instituted beginning with 1 mg. and gradually increasing the dose of daily injections to 25 mg. To this course the abscesses showed some reaction. Their discharge became more profuse and thinner as in the early stages of local infiltration.

By April, 1948, he was moribund, but a larger supply of the drug became available and in 3 weeks he was given a total of 450 mg. of prodigiosin in propylene glycol (5 mg. per cc.) intravenously. It was hoped that even though it failed of therapeutic effect, localization of the drug in granulation tissue might be determined at necropsy. He expired on May 7, 1948. Permission for necropsy was not obtained. Until he was moribund, he showed improvement whenever the drug was used.

COMMENT. Although this patient expired, we learned that the drug could be given locally, intramuscularly and intravenously without signs of toxicity in the dosage used. Until he was moribund, he showed improvement whenever the drug was used even though in small amounts, and his condition became worse whenever the drug was stopped.

CASE 2, E.Z. A 30-year-old Negro was admitted to Wadsworth General Hospital November 8, 1948, because of chest pain, fever and cough of 1 month's duration. Temperature was 101.6° F. The only pertinent physical findings were those of pneumonitis of the right lower lobe.

Laboratory examination: White cell count 11,250 with 78% polymorphs and 2% eosinophils. A chest Roentgen-ray showed bilateral lower lobe infiltrations more prominent on the right with slight hilar adenopathy The precipitin test for *C. immitis* was positive in 1:40 dilution and the complement fixation was one plus in 1:8 dilution.

Course. In April, 1949, he developed a large abscess containing *C. immitis* in the right supraclavicular fossa. The complement fixation was 4+ in 1:32 dilution and a month later, 2+ in 1:64 dilution.

On April 25, 1949, intravenous prodigiosin therapy was instituted on a daily schedule until thrombosis precluded further therapy, after 200 mg. had been given. Shortly after institution of therapy, the complement fixation was 2+ in a dilution of 1:64 and the abscess was 9 x 7 cm. in size. After therapy was discontinued on June 10, 1949, the complement fixation fell to 1+ in 1:32 and the abscess had decreased in size to 2 x 1 cm. The white cell count was 8,000 with normal differential and the sedimentation rate was 12 mm. per hour. He was discharged from the hospital to be followed in clinic.

He was re-hospitalized on August 3, 1949, because of the development of a new abscess at the lower margin of the older one. It measured 4 x 5 cm., and was possibly initiated from trauma received while playing with his children. The aspirated material contained spherules of *C. immitis* and was positive culturally. The sedimentation rate was 16 mm. corrected.

Intravenous prodigiosin therapy was again instituted and was continued until 205 mg. had been given. At this point, the only us-

able remaining superficial vein became thrombosed in spite of the administration of the medication diluted in 500 cc. of 5% glucose in water. The abscess drainage became culturally negative and gradually healed. He was continued on conservative treatment of bed rest and diet for another 6 months and was allowed to return to work in June, 1950. He is still being followed and is clinically well. His latest sedimentation rate was 1 mm. corrected and the complement fixation one plus in 1:8 dilution.

COMMENT. This is a case of disseminated coccidioidomycosis in a young Negro who at present is apparently recovered after prodigiosin therapy. He has been followed for 27 months without recurrence. There were no signs of toxicity attributable to the drug.

CASE 3, A.D. A 35-year-old white male, admitted June 23, 1949, as a known case of disseminated coccidioidomycosis with lytic lesions of the skull. He had pneumonitis in March of 1949. Physical examination showed evidence of weight loss. Temperature was 100° F. The only significant abnormality was that of pneumonitis of the right upper lobe.

Laboratory examination: Red cell count of 3,900,000, white cell count of 8,200, 79% polymorphs and sedimentation rate of 25 mm. corrected. Urinalysis was normal. A/G ratio 2.8/4.9. A chest Roentgen-ray showed widening of the mediastinum and an infiltration of the right upper lobe. Skull films showed 2 lytic areas.

Course. On August 3, 1949, intravenous therapy was begun using 5 mg. prodigiosin in propylene glycol as the daily dose. By the time he had received 185 mg., all the peripheral veins were sclerosed and therapy had to be discontinued. The only effect noted during therapy was disappearance of night sweats. Multiple abscesses developed and he expired January 27, 1950. Permission for necropsy was not obtained.

CASE 4, W.S. A 35-year-old Negro was admitted to Birmingham Veterans Administration Hospital December 30, 1948, as a known case of disseminated coccidioidomycosis. Physical examination showed subcutaneous abscesses in the right submaxillary region and in the left anterior axillary fold.

Laboratory examination: Red cell count of 5,000,000, white cell count of 8,000 with 75% polys. Urinalysis was normal. Bone survey Roentgen-ray studies showed no lesions of coccidioidomycosis. *C. immitis* was cultured from material aspirated from the abscesses, and the complement fixation test was 4 + in 1:64 dilution.

Treatment with prodigiosin was instituted on January 28, 1949. At first this consisted of infiltration of an abscess which healed completely in 1 month. Later intravenous therapy was carried out until 75 mg. had been given. Thrombosis precluded further intravenous therapy. By June 30, 1949, all abscesses had healed and the complement fixation had fallen slightly to 2 + in 1:64 dilution.

COMMENT. This patient is clinically well and serologically arrested 24 months after receiving a relatively small amount of the drug.

CASE 5, B.M. A 25-year-old Negro entered Birmingham Veterans Administration Hospital June 23, 1948, as a known case of disseminated coccidioidomycosis.

Physical examination revealed weight loss, abscesses in the right inguinal and right sternomastoid region, a granulomatous ulcer 5 cm. in diameter in the right posterior iliac region and adenopathy in the left axilla and both groins.

Laboratory examination: Red cell count 5,210,000, white cell count 20,800 with 73% polymorphs, and a sedimentation rate of 27 mm. per hour. Urinalysis was normal. The complement fixation test for coccidioidomycosis was positive in 1:256 dilution. Roentgen-ray examinations showed lytic lesions of the left ilium and the right sacrum. At a later date, there was defect seen in the left wrist. Coccidioidin skin test was positive with 1:50 dilution of coccidioidin.

Course. For 9 months he was treated conservatively with bed rest, diet, transfusions, etc. His general condition improved markedly and his complement fixation titer fell slightly to 1 + in a dilution of 1:128. Abscesses healed but new ones continued to appear.

Intravenous prodigiosin therapy was instituted on March 24, 1949, and continued until 85 mg. had been given at which point thrombosis precluded further intravenous therapy. All abscesses were healed by July, 1949, and have remained so since. His last complement fixation test was 3 + in 1:32 dilution (January, 1950). He was discharged July 5, 1949 and returned to hard labor against advice. Another patient, a friend of his, reports that he is still well and working.

COMMENT. This patient probably owes his life primarily to intensive non-specific supportive therapy. His own resistance to the disease must be considered. However, it is uncommon for one with so extensive a dissemination to recover. The diminishing titers of complement fixation indicate progressive recovery. Venous thrombosis interfered with therapy.

CASE 6, H.J. A 52-year-old white male was admitted November 7, 1949, with known disseminated coccidioidomycosis. Physical examination revealed a thin, pale, severely ill man with his left leg in traction. There was an abscess of the left thigh draining posteriorly and a draining sinus from the lower third of the right tibia. In addition, there was limitation of motion of the spine due to rheumatoid spondylitis.

Laboratory: Red cell count 3,700,000 white cell count 32,400 with 89% polymorphonuclear cells, and sedimentation rate 25 mm. per hour corrected. Urinalysis and other routine procedures were normal.

Cultures from abscess and sinus drainage were positive for *Coccidioides immitis*. Complement fixation test taken prior to admission was 1 + in a 1:32 dilution. Roentgen-rays revealed a pathological fracture of the left femur with a 7 cm. defect in the middle third; a sharply punched out lytic lesion in the lower third of the right tibia and moderate spondylitis.

Course. Because there was such an extensive abscess in the left thigh and so large a defect in the femur, amputation through the middle third was done November 23, 1949, followed 2 months later by disarticulation at the hip because of continued profuse culturally positive drainage.

Therapy with prodigiosin was instituted on February 3, 1950. This was continued over a period of 11 months during which he received 570 mg. as local infiltration of abscess and sinus, 100 mg. intravenously and 3.5 gm. orally; the latter in 10 mg. doses t.i.d. with meals. At the end of this period, he felt well, appeared clinically well and had gained 20 pounds. His complement fixation test had fallen to 1 + in 1:16 dilution. His red cell count was 5,250,000, white cell count 13,000 with 71% polymorphonuclear cells and a sedimentation rate of 10 mm. per hour corrected. His right tibial sinus had continued closed but occasional spotting continued on his left stump. This was culturally negative for *Coccidioides immitis*. Roentgen-ray studies indicated slight diminution in the right tibial lesion. He was discharged March 8, 1951, to the care of his local physician. At present he is reported well and working 5 hours a day in a wheel chair.

COMMENT. A patient with disseminated coccidioidomycosis was given 570 mg. of prodigiosin by local infiltration; 100 mg. intravenously and 3.5 gm. orally over a period of 11 months. He became clinically well; showed a drop in complement fixation titer and slight healing of a bony lesion.

CASE 7, C.S. A 34-year-old Negro was admitted March 31, 1950, as a known case of disseminated coccidioidomycosis. Physical examination revealed a 6 by 6 cm. draining abscess in the right supraclavicular fossa.

Laboratory examination: Red cell count 3,500,000, white cell count 12,000, with 78% polymorphs and 3% eosinophils. Sedimentation rate was 27 mm. per hour. Urinalysis was normal. Serum albumin 3.4 and globulin 4.5. Roentgen-rays revealed residuals of a pneumonitis in the left lower lobe, and osteoarthritis of the lumbar vertebrae. Cultures of the drainage from the neck abscess grew *C. immitis*. Complement fixation titer was 1 + in 1:256 dilution.

Course. Prodigiosin therapy was instituted April 3, 1950. 205 mg. were given intravenously before thrombosis precluded further intravenous therapy. This point was reached in early June, 1950, and by then the abscess had resolved leaving no indication for local therapy. His sedimentation rate remained elevated, however, between 25 and 30 mm. per hour corrected; and the complement fixation test rose to 3 + in 1:256 dilution. He showed little change clinically beyond the initial improvement and continued to have a low grade fever. In December, 1950, lytic lesions were found in several vertebrae and a few weeks later empyema of the left chest developed. At this point, oral administration of the drug was instituted in dosages of 10 mg. three times daily with meals. A total of 4.2 gm. was administered by May 28th when he expired after a steady downhill course.

COMMENT. This patient seemed to respond slightly to a small course of intravenous therapy but showed no ap-

parent response to a later larger dose of oral therapy.

CASE 8, A.J. A 26-year-old Negro, known diabetic, was admitted November 26, 1949, with the complaints of cough, chills and fever for 8 days. Physical examination revealed findings consistent with pneumonitis of the right lower lobe.

Laboratory examination: Red cell count 4,700,000, white cell count 7,800 with 75% polymorphs and sedimentation rate 30 mm. per hour. Repeated urinalyses showed a varying degree of glycosuria and occasionally acetonuria depending on the status of the diabetes which was difficult to control. Roentgen-ray examination demonstrated a pneumonitis in the right lower lobe. Spherules of *C. immitis* were found in his sputum. The precipitin titer of December 15, 1949, was 3 + in 1:40 dilution and the complement fixation was 2 + in 1:2 dilution. Coccidioidin skin test was negative using 1:10 dilution.

Course. By May 1950, he had developed multiple subcutaneous abscesses containing *C. immitis.* The complement fixation had risen to four plus in 1:64 dilution and the sedimentation rate persisted at 30 mm. per hour.

On May 10, 1950, intravenous prodigiosin therapy was instituted by injection into the tubing of a running 5% glucose venoclysis. He received a total of 475 mg. in 70 days without apparent influence on the coccidioidomycosis. The diabetes was not affected. Oral medication produced diarrhea and was refused.

His course was progressively downhill and he expired in May, 1951. Permission for necropsy was not obtained.

COMMENT. This young Negro diabetic developed disseminated disease rapidly with a high sedimentation rate and rising complement fixation titer. The course of the disease was rapid and he died 3 months after institution of therapy.

CASE 9, R.H. A 51-year-old white male was admitted on December 8, 1949, as a known case of disseminated coccidioidomycosis and rheumatoid arthritis. Physical examination revealed a well nourished man in mild distress with swelling and limitation of motion of both ankles, particularly the left, and draining sinus in the metatarsal areas of both feet and the ankle and heel on the left.

Laboratory examination: Red cell count, 3,900,000, white cell count 8,500 with 75% polymorphs and a sedimentation rate of 26 mm. per hour. Cultures of all draining sinuses were positive for *C. immitis.* Urinalysis was normal. Roentgen-ray studies showed marked destruction of the left ankle and the lower third of the left tibia and fibula and lytic lesions of the right fourth and fifth metatarsals. The complement fixation titer was 4 + in 1:32 dilution.

Course. Intravenous prodigiosin therapy was instituted February 28, 1950, and by April 30, 1950, he had received 500 mg. He improved clinically with disappearance of long-standing night sweats, lessening of temperature. There were no significant changes in renal or hepatic function studies associated with the period of medication and the sedimentation rate varied between 18 and 32 mm. per hour corrected.

Because there was no demonstrable improvement in the bones of the left ankle and it was useless for weight bearing, a below-knee amputation was performed on July 10, 1951. The right metatarsal defect remained but the sinus dried up except for occasional culturally negative spotting. With a prosthesis he is now fully ambulant and very active. His sedimentation rate was 19 mm./hour when last taken and his complement fixation test dropped to 1 + in 1:16 dilution.

COMMENT. This patient has returned to a very active life against advice but seems clinically arrested and has shown a slight drop in his complement fixation titer.

Discussion. Fourteen patients with disseminated coccidioidomycosis have been treated with prodigiosin. Five of the 14 were moribund at the time treatment was instituted. They were treated primarily because they had been transferred for therapy as a last resort, and also in an effort to determine a suitable means of parenteral administration.

In the remaining 9 patients a favorable clinical and serological response occurred in 6. (Numbers 1, 2, 4, 5, 6 and 9). No response was apparent in 3. (Numbers 3, 7 and 8). Six of the 9 patients were Negroes of whom 3 are apparently recovered and have been

followed for over 2 years. One Negro (case number 1, who of necessity received intermittent treatment, improved whenever the drug was given, until his last course, at which time he was moribund.) Two Negroes showed no response to the drug.

When given as a local injection, prodigiosin produced an inflammatory reaction of marked degree in abscesses of coccidioidomycosis. This persisted for approximately 48 hours. Succeeding injections were followed by diminishing reaction. The drainage thinned and increased for about 5 days following which it gradually ceased. The cultures became negative in 2 weeks and the abscesses healed in a month. It is usual for large abscesses to persist for 3 or 4 months. The reaction associated with injection of the drug into abscesses was much greater than the local reactions occurring when the drug was injected into non-diseased tissue in man or animals. The water soluble preparation, not now available, was well tolerated when given intramuscularly. The drug prepared for intravenous use produced venous sclerosis after 3 or 4 injections. Orally, in the amount of 10 mg. 3 times daily with meals, it was satisfactorily tolerated. Larger amounts produced epigastric distress or diarrhea.

No significant changes attributable to the drug have appeared in the screening tests of liver and renal function or in the studies of peripheral blood. Increased dosages have been precluded by venous sclerosis or by diarrhea. When suitable preparations are available, it would be desirable to treat the patient as soon as dissemination is determined. At this time, it does not seem advisable to treat primary cases.

Summary. Fourteen patients with disseminated coccidioidomycosis were treated with Prodigiosin. Five of these were considered hopeless at the time therapy was begun. Of the remaining 9 patients, 3 have apparently recovered, 3 have shown evidence of clinical improvement and 3 have shown no response.

From the results in our series of cases, further investigation of the use of Prodigiosin seems warranted and is being continued.

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PASTEURELLA MULTOCIDA IN SUPPURATIVE DISEASES OF THE RESPIRATORY TRACT

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Bacteria of the genus Pasteurella are familiar to physicians as the causative agents in cases of tularemia and bubonic plague. In addition to these bacteria which are capable of parasitizing man, certain species of the genus Pasteurella are responsible for epidemics of hemorrhagic septicemia in a variety of domestic and wild animals. "Shipping fever" and "fowl cholera" are terms often used to describe this type of infection. Animal species of Pasteurella frequently have been identified by naming them for their hosts. For example, those infecting birds are called "*Pasteurella aviseptica*" and those infecting bovines are called "*Pasteurella boviseptica.*" Since such a procedure has little bacteriologic support, the genus and species name, *Pasteurella multocida,* has been assigned to the heterogenous group of organisms capable of producing hemorrhagic septicemia.

Nearly all of the early recorded instances of infection of human beings with *Pasteurella multocida* have consisted of reports of isolated cases from the European continent. In 1947, Schipper[6] reviewed all cases of pasteurellosis reported in the years 1930 to 1946, inclusive. In addition, he also reviewed a case that was reported in 1919. In 21 of the more than 30 cases reviewed by this author, the diagnosis of pasteurellosis appeared to have been warranted on the basis of the bacteriologic findings.

In 8 of the 21 cases, the infection was the result of bites by animals (usually cats). The infection was localized in the extremities in most of these cases, although septicemia occurred in one case in which the infection followed a panther bite. In the remaining 13 cases, the method of infection was not obvious, and the infection was systemic in nature. The diagnosis was as follows: severe pulmonary infection in 7 cases, meningitis in 4 cases, appendiceal abscess in 1 case, and septicemia in 1 case.

Although Schipper did not mention any case of human pasteurellosis which he had observed personally, he said that he had isolated 14 strains of *Pasteurella multocida* from healthy Norway rats, which are immune to this micro-organism. He suggested the possibility that such rats might be responsible for transmitting this micro-organism to both animals and human beings.

Schipper called attention to the fact that *Hemophilus influenzae* may closely resemble Pasteurella. He said that this resemblance may account for the small number of cases of human pasteurellosis that have been reported in the literature. We have made the additional observation that the gross appearance of the colonies on nutrient

blood agar and chocolate blood agar simulates that of colonies of certain strains of Klebsiella. If additional laboratory evidence is lacking, this resemblance may account for an erroneous diagnosis in some cases.

Svendsen[7] reported a case in which an abscess of the brain was caused by *Pasteurella multocida*, and Zeller and Lepper[8] recently reported 2 cases of meningitis due to the same cause. Neter and associates[3,4] have observed 4 cases in which infection with Pasteurella of animal origin occurred in wounds. Ory, Jackson and Finland[5] reported a case in which infection with Pasteurella caused empyema, and Bartley and Hunter[1] reported a case of infection of the frontal sinus.

Since very few cases of infection of human beings with *Pasteurella multocida* have been reported in the literature, the isolation of this bacterium in a series of 37 cases observed at the Mayo Clinic in a period of 4 years and 10 months, namely, from October 1, 1946, to July 31, 1951, inclusive, seems worthy of report. One of us (Needham)[2] has reported our initial experience with 11 cases of this type of infection. These 11 cases are included in the 37 cases which form the basis of the present report. Our study of the original series of 11 cases revealed that *Pasteurella multocida* was virulent for mice and that it was susceptible to the action of penicillin. The strains of this bacterium isolated in the additional series of 26 cases had the same properties. In the present report, attention will be focused on our clinical observations in the entire group of 37 cases.

Twenty-four of the patients were males and 13 were females. Their ages ranged from 17 to 26 years. Twenty-seven of the 37 patients were either farmers or members of a farmer's family. Nearly all of the patients came from rural communities, and all but 5 came from Minnesota, Illinois, Iowa, Nebraska, South Dakota, Wisconsin and Montana. Two came from farming communities in Manitoba, and 1 was an entomologist from California.

TABLE 1.—SOURCE OF MATERIAL FOR BACTERIOLOGIC STUDY

Source of material	*Cases*
Bronchial secretions (bronchoscopy)	17
Sputum	15
Empyema fluid	2
Abscess of frontal sinus	1
Appendiceal abscess	1
Purulent drainage from infected gouty joint	1

TABLE 2.—CLINICAL DIAGNOSIS IN 37 CASES OF PASTEURELLOSIS

Diagnosis	*Cases*
Bronchiectasis	27
Bronchiectasis and empyema	2
Bronchiectasis and tuberculosis	1
Bronchiogenic carcinoma and empyema	1
Chronic bronchitis	3
Peritonsillar abscess	1
Appendiceal abcess	1
Infection of gouty joint	1

Table 1 shows the source of the material from which *Pasteurella multocida* was isolated, and Table 2 shows the clinical diagnosis in the 37 cases. It will be noted that disease of the upper or lower part of the respiratory system was present in 34 of the cases and that a peritonsillar abscess was present in another case. Most of the patients had bronchiectasis, as demonstrated by bronchographic studies. In nearly all instances there was associated infection of the accessory nasal sinuses. In 2 cases the diagnosis was chronic bronchitis. Had bronchograms been made in these cases, a diagnosis of bronchiectasis might have been established. In some of the cases in which *Pasteurella multocida* was recovered from bronchial secretions aspirated at the time of bronchoscopy, this bacterium also

was present in cultures of the sputum.

The bacterium was found to be sensitive to penicillin in a concentration of 0.05 to 0.8 unit per cc. of culture medium in all of the 35 cases in which the sensitivity to this antibiotic was tested. The sensitivity to streptomycin was tested in 20 cases. The bacterium was found to be sensitive to the following concentrations of this antibiotic: 1.5 to 6.25 micrograms (mcg.) per cubic centimeter in 11 cases, 12.5 mcg. per cc. in 4 cases, and 25 to 100 mcg. per cc. in 5 cases.

Two illustrative cases will be reported briefly.

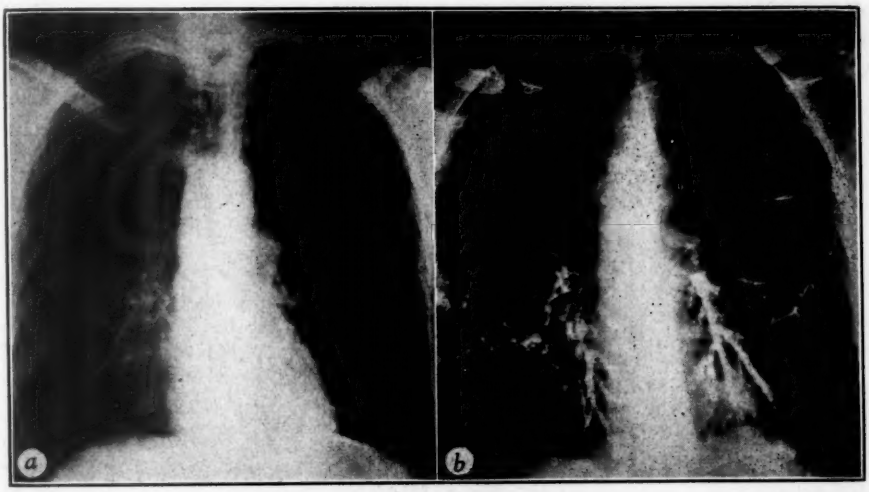

FIG. 1. *a*) Roentgenogram showing patchy infiltration of both lungs in case 1; *b*) bronchogram showing bilateral bronchiectasis in same case.

Case Reports. CASE 1. A Minnesota farmer, aged 46 years, registered at the clinic November 12, 1947. He had had a chronic productive cough for years and had raised about 4 ounces of purulent material each day. He had had repeated episodes of pneumonia. In addition to the usual mixed flora, cultures of the sputum disclosed *Pasteurella multocida* in significant numbers. This organism was sensitive to penicillin in a concentration of 0.05 unit per cc. of culture medium but was resistant to 50 mcg. of streptomycin per cubic centimeter. Stereoroentgenograms revealed a patchy infiltration throughout both lungs (Fig. 1*a*). Bronchograms revealed bilateral bronchiectasis (Fig. 1*b*). The patient was hospitalized, and penicillin was administered intensively as an aerosol for 1 week (500,000 units in 20 cc. sterile saline solution each day). Marked clinical improvement was noted. The patient's appetite increased and he gained weight. The sputum was reduced to about 10 cc. daily, and cultures of the sputum were negative for pathogenic organisms, including Pasteurella.

CASE 2. A South Dakota farmer, aged 51 years, registered at the clinic November 27, 1948. He had had pleuritic pain over the right side of the thorax in 1931 and an attack of pneumonia in 1936. He had had a chronic productive cough since 1936. Stereoroentgenograms of the thorax disclosed an empyema cavity on the right side, which was partially filled with fluid (Fig. 2*a*). Pus was aspirated from the right pleural space. Cultures of this material disclosed *Pasteurella multocida*. This organism was sensitive to penicillin in a concentration of 0.1 unit per cc. of culture medium. Bronchography disclosed bronchiectasis and a bronchopleural fistula (Fig. 2*b*). The patient was hospitalized

and penicillin was administered parenterally and in the form of an aerosol for one week. Pneumonectomy was performed on December 9, 1948, and penicillin therapy was continued. The patient made an uneventful recovery.

Comment. In cases of pulmonary suppurative disease, results of treatment are always difficult to evaluate, as there are many factors which must be taken into consideration. Despite the fact that the strains of *Pasteurella multocida* were found to be virulent for mice, we cannot assume that this bacterium was responsible for the disease process. Certainly, in cases of bronchiectasis, bacterial infection is a secondary process. The multiplicity of bacteria usually found in the secretions in cases of pulmonary suppurative disease makes it difficult to incriminate any one group of bacteria as the source of infection. However, penicillin therapy appeared to be unusually effective in the treatment of the infections encountered in this group of patients. In 12 of 13 cases of suppurative bronchiectasis in which adequate treatment with penicillin aerosol was used, a satisfactory and often striking reduction in the volume of secretions was obtained. It is true that streptomycin also was administered as an aerosol treatment in several cases in which other gram-negative bacteria, such as *Aerobacter aerogenes* and *Hemophilus influenzae*, were found. Penicillin administered parenterally and as an aerosol was effective in 4 cases of bronchiectasis in which pulmonary resection was performed. Penicillin also appeared to be helpful in 1 case of bronchiectasis and empyema in which pneumonectomy was performed. The patients who were operated upon for peritonsillar abscess, infection of the frontal sinus and appendicitis also were given penicillin with apparent benefit.

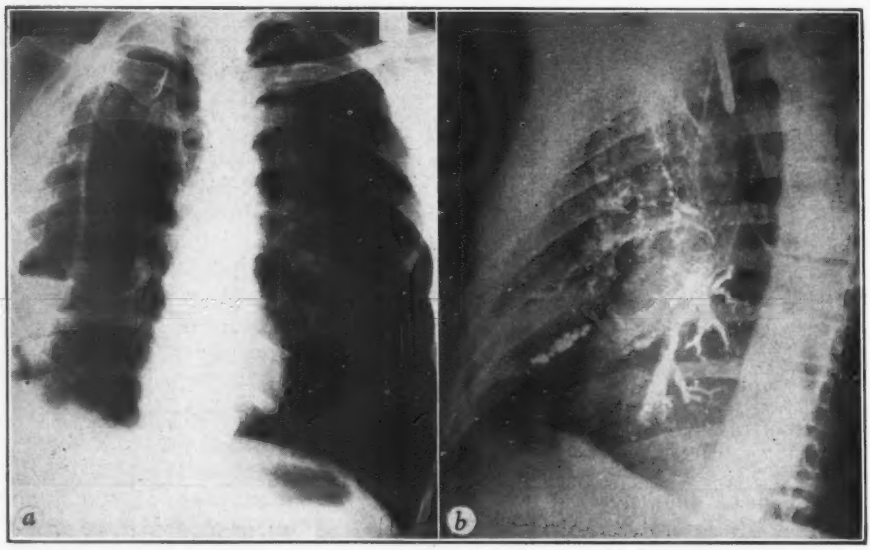

FIG. 2. *a*) Roentgenogram showing empyema cavity on right side in case 2; *b*) bronchogram showing bronchiectasis of right lung and bronchopleural fistula.

Summary and Conclusions. *Pasteur-*

ella multocida, which generally is considered to be an animal species of Pasteurella, occurs in human beings, especially in the infected secretions of the respiratory tract. Thirty-seven cases are reported herein. *Pasteurella multocida* isolated from these cases was found to be sensitive to low concentrations of penicillin. It would be unwise to assume that *Pasteurella multocida* was the causative agent of the pulmonary infections encountered. Other mechanisms are usually responsible for the development of bronchiectasis, and *Pasteurella multocida* is probably a "secondary invader," as are most of the bacteria isolated from infected bronchial secretions. Nevertheless, the finding of animal Pasteurella in cases of human disease has a definite significance. The organism is usually the predominant pathogen when it occurs in the cultures of bronchial secretions or empyema fluid. It usually occurs in persons who have ample opportunity for contact with infected animals. Furthermore, *Pasteurella multocida* is rapidly eradicated by penicillin therapy, and clinical improvement usually has been observed after the administration of this antibiotic. In view of the fact that animal Pasteurella appears to be relatively common in human infectious disease, it would be desirable that a search be made for this organism in infected material. The exact role of *Pasteurella multocida* in human disease has yet to be determined.

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HEREDITARY SPHEROCYTOSIS (CONGENITAL HEMOLYTIC JAUNDICE): PATHOGENESIS OF THE "HEMOLYTIC" CRISIS*

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Recently an uncommon opportunity to observe three young brothers** during acute "hemolytic" crises with hereditary spherocytosis revealed evidence of temporary marrow aplasia or maturation arrest, reticulocytopenia and lack of icterus. These findings offer support to the current concept of Owren[9] which states that transient marrow aplasia is the primary factor in the pathogenesis of the acute crisis and not a sudden increase of hemolytic activity. Owren presented evidence based on a study of 6 patients in 1 family with concurrent "hemolytic" crises, including 1 patient studied just prior to the onset. During the crisis he noted reticulocytopenia, leukopenia, thrombopenia, and in the marrow transient aplasia of erythropoiesis with maturation arrest of granulopoiesis.

Dameshek[3] reported observations in substantial agreement with the exception of interpretation of the marrow findings. He believed the marrow showed maturation arrest rather than aplasia and reasoned that this arrest was caused by increased "hypersplenism." He also reported the presence of abnormal iso-antibodies in 2 acute cases. Li, Voth and Osgood[6] found a definite increase of fecal urobilinogen output which reflected an acceleration of hemolysis during the crisis. This observation neither confirmed nor denied Owren's concept or the hypersplenism theory, but suggested that both play a part.

The etiology of the crisis has not been proved but considerable evidence suggests that acute infection is the important "trigger" factor.

Case Reports. Case 1. Thomas, age 12, became ill on November 22, 1950, with headache, cough and weakness followed by fever and epistaxis. Penicillin and symptomatic treatment were not beneficial. His family physician first observed pallor 7 days after the onset and admitted him to the local hospital the next day (November 30). Physical examination at that time revealed an acutely ill boy with fever, extreme pallor, anicterus, splenomegaly and inflammation of the upper respiratory tract. Blood counts confirmed the presence of anemia and a 500 cc. blood transfusion was given without reaction. The donor was the patient's father (Case 6) who later was proved to have hereditary spherocytosis. Clinical improvement began on December 3 and the patient was transferred to the Cleveland Clinic Hospital on December 7. Upon admission, he did not appear acutely ill. There was no definite evidence of respiratory infection. The oral temperature was 99.2 F., pulse 110, blood pressure 85/50. Pallor, lack of icterus and splenomegaly were apparent.

The laboratory data is recorded in Table 1. Blood smears showed a high percentage of microspherocytes. The duration of the acute illness and the reticulocyte count of 11.5% on admission suggested the boy was in the recovery phase of the crisis. Penicillin and aureomycin were administered for the first 4 days due to the cough and low grade fever even though the Roentgen-ray examination of the chest was normal.

The reticulocytes continued to rise and splenectomy was performed on December 14,

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1950, by Dr. George Crile, Jr., with a subsequent uneventful convalescence. The only blood transfusion was given on December 1.

CASE 2. Robert, age 7, became ill on November 30, 1950, with symptoms of an upper respiratory infection, cough and earache followed in a few days by nausea, vomiting and conspicuous pallor. A blood count at home, on December 3, revealed anemia. Previous illnesses recalled by the mother were measles, whooping cough, mumps and ear infections. Neither pallor nor jaundice had been observed prior to the recent illness.

On admission to the Cleveland Clinic Hospital, December 8, 1950, the child appeared acutely ill, lethargic, and pale without jaundice. The rectal temperature was 101 F., pulse 108, blood pressure 82/32. Labial herpes simplex, subacute left otitis media and evidence of subsiding upper respiratory infection were noted. The spleen was palpable and nontender at the edge of the costal margin. The remainder of the physical examination was normal.

The chest Roentgen-ray was normal. The laboratory data is recorded in Table 1. The blood smears revealed a high percentage of microspherocytes and a mean red cell diameter of 6.0 microns.

The fever subsided in 48 hours. Penicillin and aureomycin were given for the first 5 days. Blood for transfusion was readily available but not given in order to study the natural course of the crisis. Clinical and hematologic improvement began on December 11 with the reticulocyte count rising to 17.8% and the appearance of normoblasts in the peripheral blood smear. Improvement continued and splenectomy was performed on December 18, 1950, with an uneventful postoperative course.

CASE 3. Charles, age 6, became ill with similar symptoms on November 30, 1950, the same day as his brother Robert. A low grade fever persisted for the first 5 hospital days in spite of penicillin and aureomycin. A history of allergic bronchial asthma was obtained but he was free of attacks at this time. The child's mother denied evidence suggestive of pallor or jaundice prior to this illness.

Physical examination disclosed pallor, splenomegaly, and evidence of an upper respiratory infection. Charles did not appear as ill as his brothers. Clinical and hematologic improvement began on December 11. Splenectomy was performed on December 18 with an uneventful postoperative course. No transfusions were given at any time. The hematologic data is recorded in Table 1.

CASE 4. The oldest brother, Paul, age 16, was not under observation during his acute illness. He became ill on October 26, 1950, with fever, vomiting and diarrhea. Four days later he was seen by his family physician who noted the presence of fever and pallor. He remained in bed for 10 days and was treated with oral penicillin for "intestinal influenza". He gradually recovered and regained his strength 3 weeks after his illness. His parents denied the presence of jaundice during his illness. Physical examination on January 25, 1951, revealed neither pallor, clinically detectable jaundice, nor splenomegaly. The blood studies of the same date (Table 1) confirmed the diagnosis of hereditary spherocytosis. Splenectomy was performed on November 12, 1951.

CASE 5. Rose Marie, age 10, presented no history of significant recent illness. The physical examination, on January 25, 1951, was normal as were the blood studies (Table 1).

CASE 6. Mr. William, age 42, father of the previously mentioned children, denied the presence of anemia, jaundice and gallbladder trouble. Physical examination revealed slight icterus of the skin and sclerae. The spleen was not palpable. Roentgen-ray examination of the gallbladder failed to show calculi. The blood studies, on December 22, 1950, confirmed the diagnosis of hereditary spherocytosis. (Table 1). The blood studies of the mother of the children were normal.

CASE 7. Mr. Theodore, age 65, paternal grandfather of the children was referred to the Clinic in April 1949, due to nervousness, mental depression and the possibility of a brain tumor. The patient mentioned that in 1948 his family physician told him his "white blood cells were too high". Blood smears revealed microspherocytes and complete blood studies confirmed the diagnosis of hereditary spherocytosis (Table 1). On careful reexamination of the abdomen, the tip of the spleen was palpable 2 cm. below the costal margin. Further direct questioning disclosed that many of his relatives and descendants had "yellow trouble and spleen trouble".

Comment. ETIOLOGY OF THE CRISES. The history obtained from the parents suggests these were the first "crises" occurring in the 4 brothers. Each of the children had made satisfactory recovery from such illnesses as measles, mumps and whooping cough without complications.

TABLE 1

	Days after onset acute illness	Date	Hb% 15.4 Gm. = 100%	R.B.C. Millions /C.mm.	W.B.C. Thousands /C.mm.	Granulocytes %	Reticulocytes %	Icterus index	Fragility hypertonic saline % NaCl	Platelets Thousands /C.mm.	Mean red cell diameter microns *	Mean red cell thickness microns	Volume thickness index	** Urobilin units /2½ hrs.	*** Blood uric acid mg. per 100 cc.	Blood urea mg. per 100 cc.
CASE 1	16	12- 8-50	44	3.28	5.8	63	11.5	6	0.66→ 0.28		6.4	2.24	1.38			
Blood Group A	17	12- 9-50	44				13.5									
Rh neg.	19	12-11-50	49		6.6	77	16.0	7		300				1.9	2.0	24
	20	12-12-50	45		4.7	61	17.2									
	21	12-13-50	46		4.8	70	17.7	7		440				1.85	1.9	24
Splenectomy→	22	12-14-50	44		4.4	67	15.8							2.66		
	23	12-15-50	55		27.8	90	15.0	5							1.8	21
	24	12-16-50	52		38.2	93	12.0									
	26	12-18-50	62		10.7	80	18.0	4								
	27	12-19-50	64				13.0									
	28	12-20-50	64				15.0									
	29	12-21-50	71	4.87	10.4	61	11.0	4	0.60→ 0.28		6.9	2.12	1.18		0.3	
	30	12-22-50	70				11.0									
	31	12-23-50	75				6.0									
	64	1-25-51	78	4.98	23.6	47	0.8	4	0.54→ 0.30		6.9	2.12	1.21			
CASE 2	7	12- 7-50	26	1.7	6.2	39	0.4	6	0.64→ 0.36		6.0	2.27	1.48			
Blood Group A																
Rh pos.	9	12- 9-50	22				0.7									
	11	12-11-50	26		16.4	79	17.8	4		360				12.7	3.5	21
	12	12-12-50	29		15.1	75	37									
	13	12-13-50	29		8.6	76	34	5		360				1.4	2.6	27
	14	12-14-50	34		5.8	64	22							3.1		
	15	12-15-50	39		5.8	64	17	5						3.8		
	16	12-16-50	42		7.2	70	11							2.4		
Splenectomy→	18	12-18-50												4.5		
	19	12-19-50	49				15									
	20	12-20-50	54				27							2.4		
	21	12-21-50	55	3.74	28.7	91	21	4	0.60→ 0.28		6.6	2.21	1.32	0.3		
	22	12-22-50	52		20	87	13									
	23	12-23-50	57				10									
	56	1-25-51	68	4.48	11.6	46	0.5	4	0.56→ 0.28		.5	2.40	1.47			

Case 3 Blood Group O Rh pos.	7	12- 7-50	32	2.27	11.4	35	0.5	6	0.64→ 0.36		6.0	2.35	1.52			
	9	12- 9-50	26													
	11	12-11-50	24		19.5	73	0.8			450						
	12	12-12-50	24		36.4	74	5.7									
	13	12-13-50	27		25.8	79	13.1	3		480				3.9	2.2	27
	14	12-14-50	34		10.0	68	27.6							5.4		
	15	12-15-50	40		8.1	73	32	6						4.1	1.8	33
	16	12-16-50	42		12.0	78	17							2.6		
Splenectomy→	18	12-18-50	49		5.3		25							8.0	2.2	
	19	12-19-50	51				20									
	20	12-20-50	54				32							0.4		
	21	12-21-50	58	4.19	9.4	70	19	4	0.64→ 0.28		6.6	2.27	1.35	2.5		
	22	12-22-50	58				12									
	23	12-23-50	62				9.4									
	56	1-25-51	71	4.59	15.1	54	0.3	4	0.56→ 0.30		6.7	2.24	1.32			
Case 4	91	1-25-51	71	4.58	8.5	48	8.3	12	0.66→ 0.30		6.1	2.61	1.68	No splenectomy performed		
Case 5	Not ill	1-25-51	71	4.5	6.5	44	0.1	4	0.44→ 0.30		7.7			No evidence of spherocytosis		
Case 6	Not acutely ill	12-11-50	70	4.42	12.4	76	13.8	8	0.66→ 0.34		6.1	2.74	1.78	No splenectomy performed		
Case 7	Not acutely ill	4-13-49	78	4.5	6.7	69	7.1	12	0.64→ 0.30		6.7	2.34	1.38	No splenectomy performed		

* Haden Erythrocytometer ** Watson method *** Folin-Wu method

The mother seemed to be a careful observer and denied the presence of pallor or jaundice in any of the children prior to the recent illness. The dates of the onset of the illness are as follows:

Paul	Case 4	October 26, 1950
Thomas	Case 1	November,22, 1950
Robert	Case 2	November 30, 1950
Charles	Case 3	November 30, 1950
(Richard, first cousin,		December 8, 1950)*

This indicates a spread of 5 weeks in the onset of the "crises". The onset of illness in each child was abrupt so that the specific date could be determined. Other members of the immediate family, that is, the father, mother and daughter gave no evidence of illness nor infection during this time. The father, Case 6, later proved to have the chronic active form of hereditary spherocytosis, remained free of symptoms during the entire period.

Upon admission to the hospital, nasal and pharyngeal smears and cultures of the three children failed to reveal pathogenic bacteria. Unfortunately, sera for agglutination–inhibition tests against strains of influenza virus were not taken until December 22, which was several weeks after the onset of the illness.** Since no sera were obtained at the time of the acute illness, no conclusions regarding recent influenza infection could be drawn from these studies.

The concurrent crises in the 5 children with an incubation period of 8 or more days suggests that a viral respiratory infection precipitated the crises. Singer[11] recently presented convincing evidence that acute infection initiated crises in sickle cell anemia and one is inclined to draw an analogy in these hereditary hemolytic diseases.

Dameshek[2] has emphasized that the symptoms of fever, tachycardia, headache, abdominal pain, nausea, and vomiting may be due to the acute anemia and not infection and are also observed in many patients with acute acquired hemolytic anemia.

Hematologic Events in the Acute Crisis (Figs. 1, 2, 3). The initial blood studies in Cases 2 and 3 revealed profound anemia with a high percentage of microspherocytes, reticulocytopenia, and normal icterus indices. The mean red cell diameter was 6.0 microns, reflecting the severe degree of spherocytosis. The marrow obtained by iliac aspiration was hypocellular in both cases, revealing a preponderance of granulocytic cells and conspicuous decrease of late erythroblastic cells. The differential counts of the erythroid cells are given in Table 2, and confirm the impression of hypoplasia of the erythroid cells and maturation arrest at the proerythroblast stage. These marrow changes explain the pronounced reticulocytopenia noted in the acute phase. The abrupt and apparently spontaneous increase of reticulocytes which occurred several days later paralleled the finding of many late erythroblasts in the marrow at this time. A distinct granulocytosis preceded the increase of the reticulocytes. The blood smears revealed many nor-

* This first paternal cousin and playmate of the 3 young brothers was not observed during his acute illness. Information from the relatives described his illness as similar to his cousins with fever, pallor, etc. He was hospitalized near his home and given multiple transfusions until recovery. In April 1951, blood smears of the child and his mother revealed microspherocytes and mean red cell diameter of 6.4 and 6.6 microns respectively. Splenectomy was performed at the Cleveland Clinic Hospital in August 1951.

** Appreciation is expressed to Dr. William S. Jordan, Department of Preventive Medicine, School of Medicine, Western Reserve University, for this data and his evaluation of the results.)

moblasts. Following the reticulocyte response the anemia showed rapid improvement. The icterus index varied between 4 and 6 during the entire period. An unfortunate misunderstanding prevented quantitative fecal urobilinogen determinations. There was no evidence of hemoglobinemia or hemoglobinuria during the illness. The Coombs tests were repeatedly negative. No significant variations were noted in the platelet count, blood uric acid or blood urea.

Case 1 was first seen in the recovery phase of the acute crisis as noted by the reticulocyte increase from 11.5% to 17%. This child was given a 500 cc. blood transfusion from his father one week before the initial blood study on December 8. The influence of the transfusion of microspherocytes from the affected father is not clear as regards the patient's recovery from the crisis, but the clinical course was similar to that of his brothers.

Following splenectomy the reticulocytes gradually decreased and were below 1% 6 weeks later, a response similar to that obtained in the chronic active form of the disease.

These observations are similar to those of Owren[9] and seem to refute the older concept of increased hemolytic activity as the primary factor in the mechanism of the crises. Singer *et al.*[11] has observed transient marrow arrest during crises in sickle cell anemia and this suggests that such crises have a common pathogenesis.

DATE	GRANULOCYTE TO ERYTHROBLAST G:E RATIO	PRO-ERYTHROBLASTS %	NORMOBLAST "A" %	NORMOBLAST "B" %	NORMOBLAST "C" %
CASE 2					
12-8-50	6:1	17	65	14	4
12-11-50	1:1.5	2	12	54	32
12-20-50	1:5.1	1	8	65	26
CASE 3					
12-8-50	9:1	82	12	4	2
12-11-50	1:1	2	13	63	22
12-20-50	2.5:1	1	3	78	18
CASE 1					
12-8-50	1:1.5	4	19	46	31
12-20-50	2.3:1	1	15	69	15

TABLE 2.—Differential of erythroid cells and granulocyte: erythroblast ratio in serial marrow aspirations.

Discussion. The etiology of the acute crisis remains unknown. Crises are more often observed in children and several reports[1,10] have noted concurrent familial crises. Infections of the respiratory system have been repeatedly suggested as the "trigger" of such attacks. The occurrence of the crisis in several members of one family and occasionally in neighboring relatives with "incubation" periods of

a few days or weeks between cases is presumptive evidence that infection may precipitate the attack. Influenza has been suspected, but no convincing proof has been offered to date[4,5].

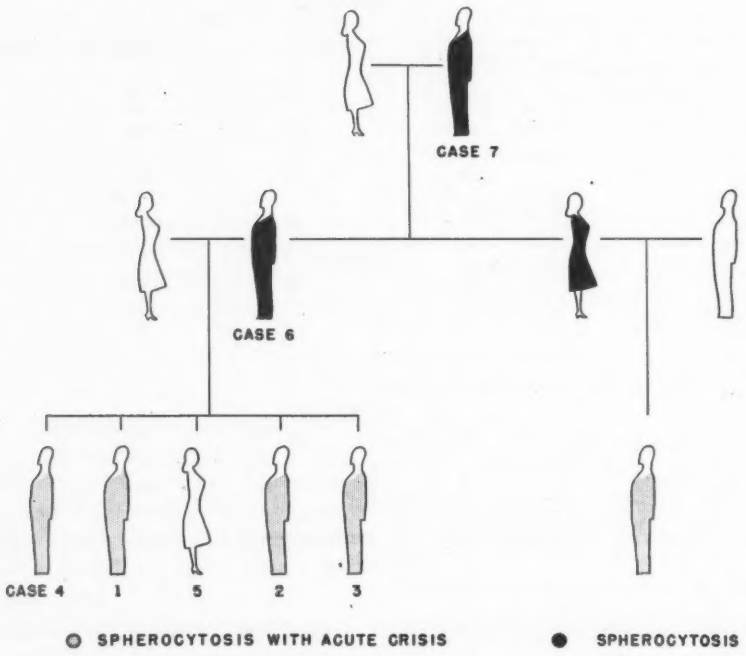
In addition, Owren[9] showed by the Ashby technique the average life span of the spherocytes in this disease to be about 15 days. Therefore, with temporary cessation of red cell formation, the red blood count would be reduced approximately one-half in about 7 or 8 days. The profound microspherocytosis and exceptionally low mean red cell diameter observed during the height of the crisis may be explained by the absence of reticulocytes at this time.

Dameshek[3] in a recent report presents evidence of a maturation arrest of all marrow elements during the crisis which he believes is primarily the result of "hypersplenism". It is difficult to evaluate the importance of "hypersplenism" in the acute crisis because of the apparent spontaneous recovery from crisis prior to splenectomy.

There is no uniformity of opinion regarding the management of patients in acute crisis. Some advise multiple transfusions and early splenectomy; others advocate caution in giving transfusions because of the reported frequency and severity of transfusion reactions.

The treatment of the 3 children in this report was based on the assumption that spontaneous recovery from the crisis would occur in a period of several days. A review of the reported cases of acute crises failed to estab-

GENETIC CHART



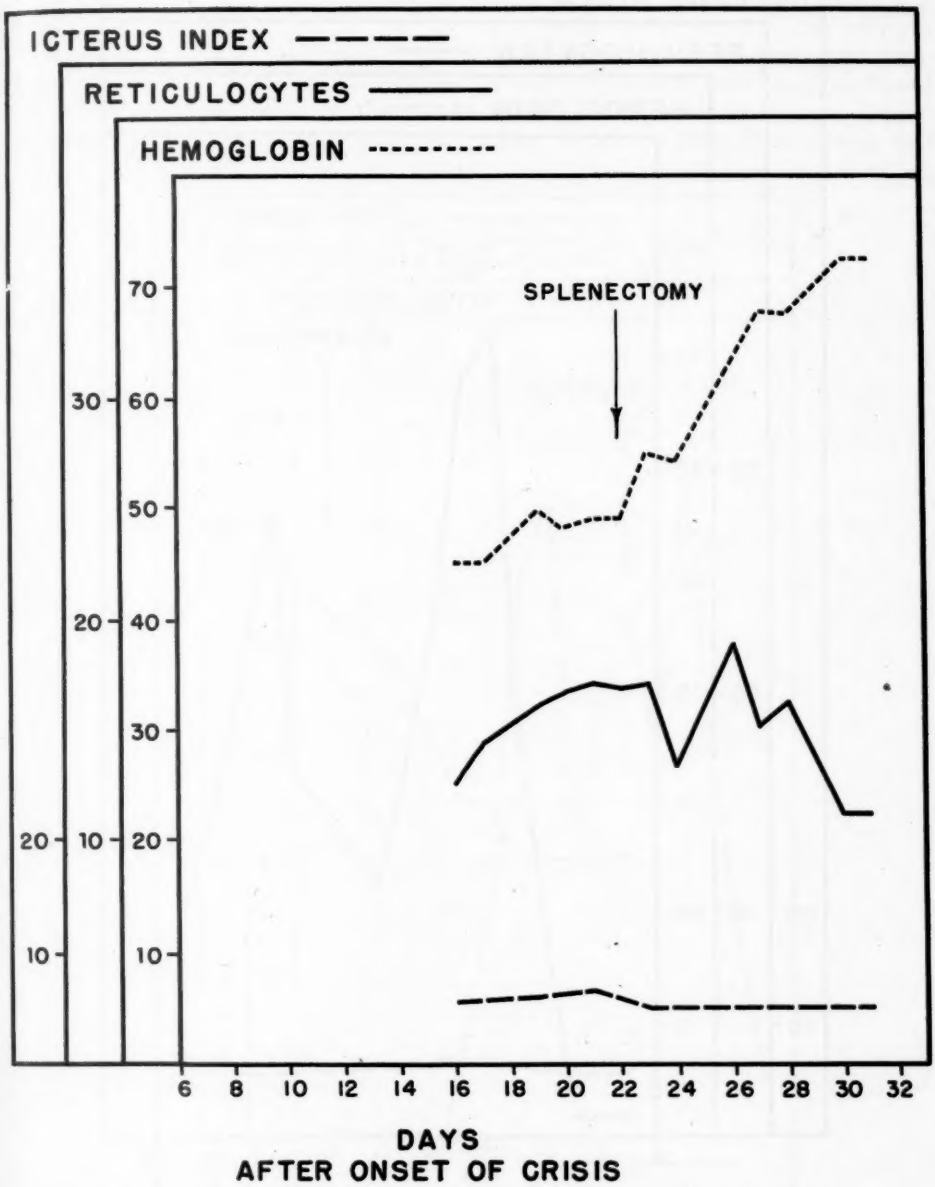


FIG. 2.—Case 1. Graph of hematologic events in acute crisis (see text).

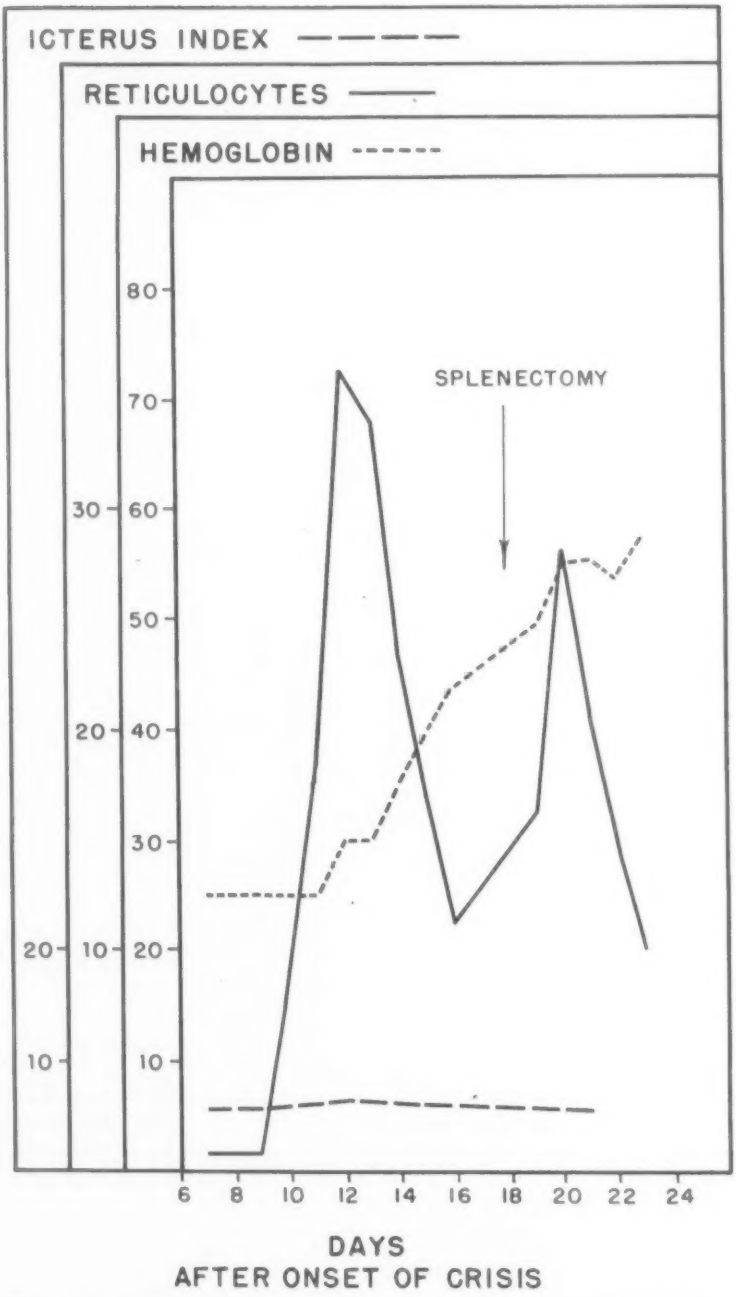


FIG. 3.—Case 2. Graph of hematologic events in acute crisis (see text).

lish the fact that transfusions hastened recovery from the crisis[3,9]. Transfusions were not employed in the treatment of these cases except in Case 1.

Splenectomy was deferred until signs of clinical recovery, resumption of normal erythropoiesis of the marrow, and reticulocytosis had occurred. The evidence suggests that the risk of splenectomy during the stage of acute crisis is unduly increased. Theoretically it would seem unwise to perform splenectomy in the presence of a profound reticulocytopenia and erythroid hypoplasia or maturation arrest. Dameshek[3], however, offers the concept that

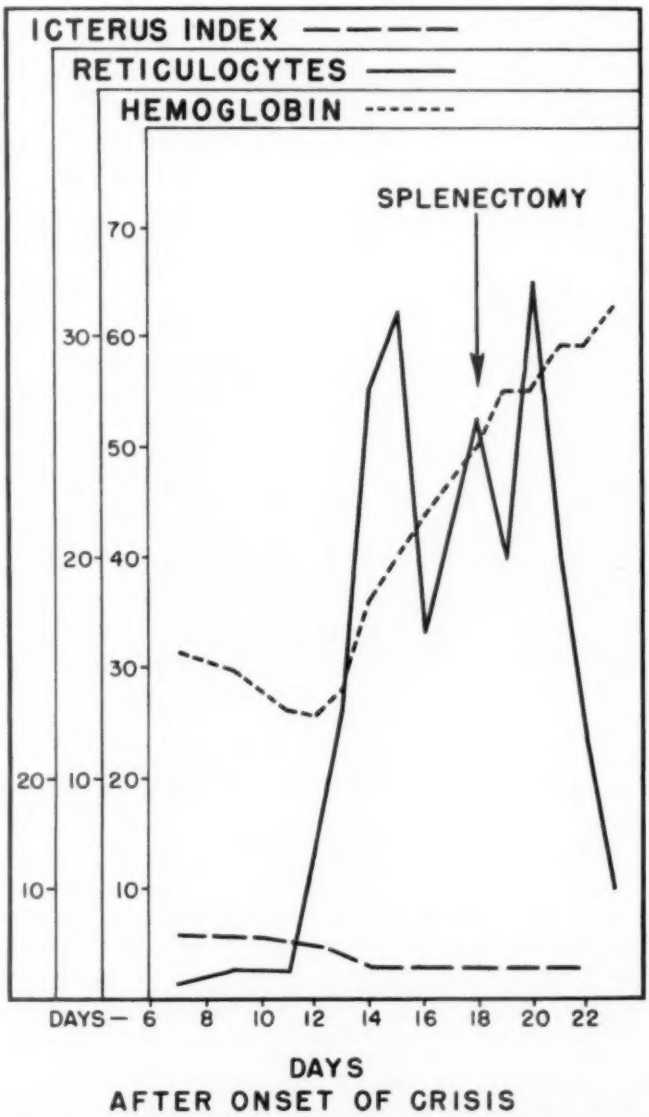


FIG. 4.—Case 3. Graph of hematologic events in acute crisis (see text).

removal of the "hypersplenic" effect on the maturation arrest of the marrow may effect a more prompt recovery. It is difficult to evaluate the hematologic results of splenectomy during the acute crisis because of the multiple transfusions given at such a time.

Summary. Clinical and hematologic events are reported which occurred during concurrent "crises" in three brothers with hereditary spherocytosis. The reticulocytopenia, absence of jaundice and temporary erythroid hypoplasia tend to support the recent proposal of Owren that the term "aplastic crisis" replace the term "hemolytic crisis".

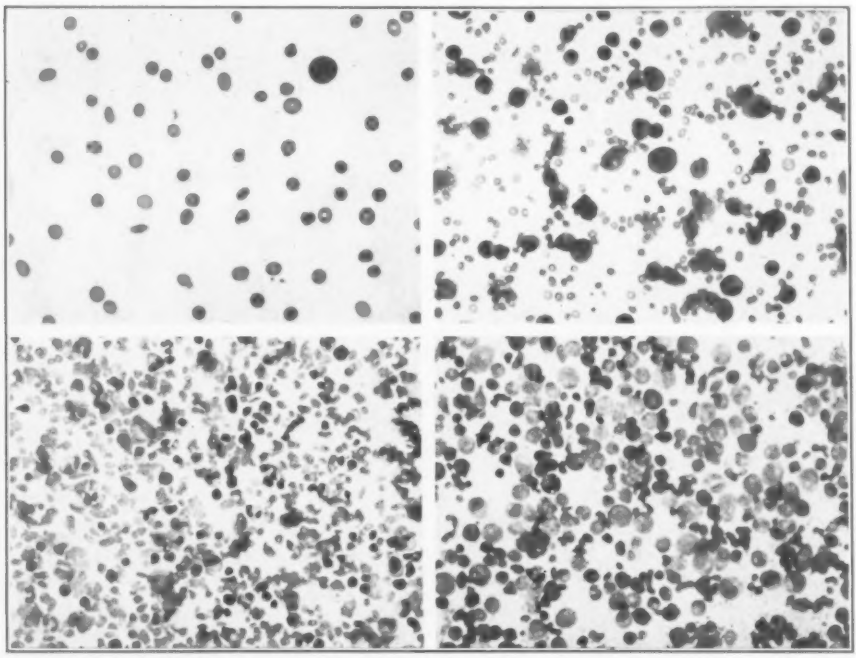


FIG. 5.—Case 2. (a) Peripheral blood smear (x350) showing marked degree of spherocytosis. (b) Marrow smear (x250); eighth day after onset of illness showing erythroid hypoplasia. Reticulocytes 0.7%. (c) Marrow smear (x250); eleventh day after onset of illness showing resumption of erythropoiesis. Reticulocytes 17%. (d) Marrow smear (x250); twentieth day after onset of illness showing erythroblastic hyperplasia. Reticulocytes 27%.

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THE COXSACKIE VIRUSES AND HUMAN DISEASE

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THE Coxsackie viruses constitute an antigenically and biologically heterogeneous group of infectious agents of small particle size[42,47] whose existence has only recently been recognized[17] and whose definitive relation to human disease remains to be determined. The criteria which distinguish the Coxsackie viruses from all other known viruses are their capacity to produce clinically manifest disease in infant mice and hamsters and their avirulence for adults of these species, except under special conditions[22,29,46].

The initial recovery, by Dalldorf, Sickles *et al.*[17,18], of viruses pathogenic for suckling mice from the feces of two children of the town of Coxsackie, N. Y., posed a problem which continues to confound the investigation of Coxsackie virus disease, that is, the etiologic relation of the recovered viruses to the illnesses of patients yielding them. Originally selected on clinical grounds as probable sources of poliomyelitis virus, these two children, both paralyzed, were then found to have been infected with viruses antigenically and pathogenetically different from poliomyelitis virus. That the new virus had actually infected one of the patients was proved by the demonstration, in his convalescent serum, of neutralizing antibodies to the virus not detectable in serum obtained early in illness. Thus, it was established early that typical poliomyelitis might occur coincident with infection by this previously unrecognized virus. The subsequent discovery that both original Coxsackie patients were infected as well with poliomyelitis virus[11] has concomitantly reaffirmed the specificity of the poliomyelitis syndrome and temporarily abrogated the role of the Coxsackie viruses in human paralytic disease. The birth of the Coxsackie virus was therefore a fortuitous event which resulted from an attempt to recover poliomyelitis virus in an unusual experimental host (the suckling mouse) from a disease state whose

specific etiology had supposedly been established 38 years previously[31]. With notable caution, Dalldorf and associates[18] emphasized promptly in their second report that the isolation of the new virus from patients whose disease states had been clinically diagnosed as poliomyelitis did not seem to warrant etiologic conclusions, as no attempt had yet been made to recover the virus from patients with other diseases.

However, the initial association of the Coxsackie and poliomyelitis viruses inevitably influenced the direction of early investigations of the relation of the new viruses to human disease. Soon after discovery of the viruses by Dalldorf and Sickles[17], Melnick, Shaw and Curnen[43] were successful in recovering apparently similar viruses from the feces of patients in whom a diagnosis of nonparalytic poliomyelitis or aseptic meningitis had been made in southern New England. Included also in this important report was evidence that a primate species (the chimpanzee) could be unapparently infected with the virus and that man might incur infection in the laboratory associated with the development of specific neutralizing antibodies and recovery of virus from nasopharyngeal washings as well as feces. Furthermore, it was shown that the new virus was present in the sewage of cities not only in the New England area but also in North Carolina, and that house flies, trapped in such widely divergent regions as New England, North Carolina and Texas, yielded Coxsackie virus, sometimes in association with poliomyelitis virus. The distribution of Coxsackie viruses thus constituted another similarity to poliomyelitis virus, which led to the adoption by the lay press of the term "poliomyelitis-like viruses." So stigmatized by superficial resemblance and bearing a formidable name, the Coxsackie viruses will probably continue to be considered "polio-like" until their role in human illness has been clarified.

The first suggestion that the Coxsackie viruses might be associated with diseases other than poliomyelitis-like syndromes was made by Curnen and associates[10], who described the recovery of virus from a young boy considered to have epidemic pleurodynia, and also from a subject with a mild "undifferentiated" febrile illness resulting from accidental laboratory infection. Subsequently, the reinvestigation by Kilbourne[28] of an undiagnosed epidemic of febrile disease affecting physicians of the Rockefeller Institute in 1948 resulted in the recovery of a strain of Coxsackie virus antigenically similar to the Yale virus (Conn 5) previously isolated from "nonparalytic poliomyelitis" and pleurodynia and demonstrated viral antibody increases in all patients studied, including one patient with typical pleurodynia. This study stressed the diversity of clinical manifestations attending infections with a single strain of Coxsackie virus and the lack of resemblance of the illnesses to poliomyelitis. Clinically unapparent infection of a laboratory worker was proved by demonstration of a rise in serum neutralizing antibodies following contact with the virus.

Meanwhile, studies by Howitt[24] of 5 geographically scattered, clinically dissimilar epidemics suggested the etiologic role of Coxsackie viruses in these cases. Evidence in these studies that Coxsackie viruses were recovered from human tissues removed at autopsy and from the blood of patients is subject to guarded interpretation in view of data presented by the investigator indicating widespread contamination of the laboratory with virus. Among patients studied by Howitt and co-workers were those of Webb and Wolfe[55], who had

previously investigated an outbreak in Louisiana of an obscure disease of children termed "three-day fever"[36]. A similar and previously defined clinical entity known as "herpangina" was then shown by Huebner and associates[26] to be associated with the presence of Coxsackie viruses (of 6 different antigenic types) in the feces and throat swabbings of ill children in Maryland. The extensive epidemiologic investigations of Huebner's group revealed the epidemic character of this disease, the occurrence of contact and convalescent carriers of virus, and the infrequent recovery of viruses from persons outside the epidemic area and from those with other, miscellaneous diseases[9].

The probable world-wide distribution of the Coxsackie viruses has been suggested by recent reports of recoveries of virus in Alaska[2], Sweden[54], France[34], England[19], Canada[48], and Holland[49]. Although 5 years of intensive study have defined the extent of the Coxsackie virus problem, little is known of the importance of the virus in human illness. The present report will endeavor to assess critically the evidence relating Coxsackie virus infection to human disease.

The Coxsackie Viruses. The biologic properties which define the Coxsackie viruses are virulence for immature mice and hamsters and relative avirulence for adults of either species[12,29]. This unusual age limitation of susceptibility probably explains previous failures to recover these viruses from human materials inoculated into commonly employed experimental animals. The increased susceptibility of young animals to viral infections has long been recognized[1,5,33], but earlier studies rarely employed mice younger than two weeks of age[30]. Newborn mice are most desirable for propagation of Coxsackie viruses, and certain strains fail to produce disease in mice more than 3 days of age[7].

That the resistance of mature mice to infection is not absolute has been demonstrated by the studies of Kilbourne and Horsfall[29], who were able to induce lethal infection of adult mice by administration of cortisone and who, by this method, recovered virus from a specimen of stool. Shortly thereafter, Pappenheimer and associates[46] reported passage of the Conn 5 strain of Coxsackie virus in adult mice and localization of disease in these animals to the pancreas. Morbidity and mortality in these mice were variable, however, and histologic examination was sometimes necessary to demonstrate infection. More recently, Graham and co-workers[22] have reported the synergistic effect of Roentgen irradiation and cortisone upon the pathogenicity of Coxsackie virus in adult mice. Serial propagation of Coxsackie virus in mouse embryo tissue culture has been reported by Slater and Syverton[51]; the recent indication that the viruses may multiply in human tissue culture[58] is of special interest, in view of the lack of direct evidence that Coxsackie viruses actually multiply in human tissue. Infection of lower primates has been demonstrated by Melnick and associates[41, 43], but disease of these animals (chimpanzees[43] and cynomolgus monkeys[41]) is not clinically manifest, and characteristic lesions have not been observed.

The pathology and pathogenesis of experimental infection of young mice with Coxsackie virus has received considerable attention[12,18,20,21,38,44,45]. Dalldorf[12] has suggested the classification, on this basis, of viral strains into Groups A and B, depending upon the histopathologic reaction which they induce in infant mice. Infection with Group A viruses results in severe, generalized myositis; in contrast, Group

B infection is associated with inconstant, scattered, focal lesions of the muscles and central nervous system as well as necrosis of fat pads[12,20]. Whereas mice inoculated with Group A viruses die with flaccid paralysis soon after sickening, disease in mice infected with Group B viruses may be more subtle and protracted and is often characterized by tremor and spasticity, dyspnea and cyanosis[12,20,27]. These details seem worthy of emphasis here because of the possibility that Group A and B viruses may induce different disease in humans. Furthermore, evidence that viruses of the two groups may also differ in particle size[47] suggests that Group A and B viruses may be dissimilar viruses with little in common save their mutual requirement of an immature murine host. To date, at least 10 antigenically distinct Group A viruses and 4 Group B viruses have been categorized by Dalldorf[15].

The Coxsackie Viruses and Poliomyelitis. Certain recently observed epidemics of poliomyelitis have been temporally and geographically associated with serologically proved Coxsackie virus infection[12,16,40], and isolation of both poliomyelitis and Coxsackie viruses from the same patient has occurred with astonishing frequency[9,12,40,48]. Although carriage of Coxsackie[8] and poliomyelitis[23] viruses may persist long after subsidence of the acute illnesses associated with either, demonstration of simultaneous antibody responses to both agents[39] has provided indirect but convincing evidence that coincident infection of the same individual with both viruses may occur. In a study of a Pennsylvania epidemic in which there was a high percentage of paralytic disease, Melnick and associates[40] recovered poliomyelitis virus from the stools of 75% of patients examined and Group A strains of Coxsackie virus from 64% of fecal specimens obtained during the acute phase of illness. In the stools of more than half of 36 patients both viruses were found. The question was raised whether simultaneous infection with both viruses ". . . tips the balance in favor of paralysis[40]." Conversely the low incidence of paralytic illness in previous epidemics of poliomyelitis associated with concomitant infection with Group B Coxsackie viruses suggested to the authors that the latter infection might ". . . limit the spread of poliomyelitis virus within the body[40]." Experimental evidence of interference of this sort has been reported by Dalldorf[13] to occur in mice infected with the Lansing strain of poliomyelitis virus and a Group B strain of Coxsackie virus. Similar interference was not demonstrable in earlier studies in primates, however[37]. Recently, Dalldorf[15] has emphasized the low incidence of paralytic poliomyelitis during a Swedish outbreak of pleurodynia.

In assessing the importance of dual infections in the enhancement or modification of poliomyelitis, one must realize that little is known of the epidemic periodicity (if such exists) of Coxsackie virus infection and that an epidemic of infection with Group A virus strains has already been shown to occur in the absence of concomitant epidemic poliomyelitis[8]. In view of the similar seasonal incidence of infections associated with poliomyelitis and Coxsackie viruses and the coincidence of distribution of both viruses in nature, fortuity cannot now be excluded in evaluating their coincident occurrence in human disease, and the stimulating speculations of Melnick and Dalldorf await further elucidation.

Herpangina and "three-day fever." During the summers of 1946, 1947 and 1948 in northern Louisiana, Webb and Wolfe observed the epidemic occur-

rence of an acute febrile illness in children which was characterized by high fever, headache, and brief duration ("three-day fever")[55,56]. From two victims of the 1948 epidemic Howitt[55] recovered viruses later classified as Group A, type 2, strains of Coxsackie virus and demonstrated an antibody response to the virus in one patient. It is of interest that the clinical paper published by Webb and associates[56] prior to the demonstration of probable Coxsackie virus etiology described "vesicular studding over the soft palate or pharynx" in a number of children. This same clinical observation was later emphasized by Huebner and associates[26] as pathognomonic of a well-defined syndrome, "herpangina," described and named by Zahorsky in 1924[59].

An epidemic of herpangina in a Maryland surburban community in the summer of 1950 was investigated by Huebner and his associates[26], who described a clinical picture reminiscent of the "three-day fever" of Louisiana but who emphasized the occurrence in patients of throat vesicles and small, punched-out pharyngeal ulcers. It is notable that Group A strains of Coxsackie virus were recovered from 32 of 37 patients studied, and specific antibody response was demonstrated in 4 of these patients in whom it was sought and in 15 other patients with herpangina mentioned in a subsequent publication[3]. The type 2 strain recovered from the patients in Louisiana was one of 6 antigenic Group A types recovered from patients with herpangina, further suggesting the identity of the syndromes of herpangina and "three-day fever."

An important contribution of Huebner's group was their epidemiologic surveillance, for almost a year prior to the outbreak, of the community in which herpangina occurred[26]. During this preceding period it was demonstrated that Coxsackie viruses were not detectable in the population of the community, even during the occurrence of sporadic febrile illnesses. Thus, the temporal association of virus isolations and the epidemic of herpangina appeared highly suggestive of an etiologic relationship of the Coxsackie viruses to the syndrome.

Epidemic Pleurodynia and Aseptic Meningitis. Like herpangina, epidemic pleurodynia or Bornholm disease is a distinct clinical entity recognized long before the discovery of the Coxsackie viruses[35,52]. The distressingly severe thoracic pain characteristic of this condition has earned it the colorful sobriquet of "devil's grip." Typically, epidemics occur in summer and principally afflict young adults and children[6]. Illness is apparently benign, and fever and malaise are of brief duration.

Since the initial recovery of a Group B strain of Coxsackie virus from a patient with pleurodynia[10], considerable evidence has accrued that Coxsackie virus infection, particularly with Group B strains, is etiologically related to the syndrome. From epidemics in New York[28], Boston[57], and the vicinity of Seattle[32] viruses have been recovered and specific antibody responses in patients have been demonstrated. Isolations of virus from patients with pleurodynia in Sweden[14] and Holland[49] have recently been cited, and British authors[19,53] have stressed the probable role of the Coxsackie viruses in the causation of the disease. Thus far, only Group B strains of virus have been associated with the naturally occurring disease.

In view of previous clinical evidence that epidemics of pleurodynia were often attended by signs and symptoms of neurologic disease[6,36], the concomitance of aseptic meningitis and pleurodynia in New England in 1948 is

notable in that the same strain of Group B virus (Conn 5: Dalldorf, Group B, type 1) was recovered from patients with either clinical syndrome[10]. Viruses similar to Group B strains were recovered during an epidemic in 1950 in a boys' camp in New Jersey, in which illness was characterized by pleocytosis of the spinal fluid and classical signs of pleurodynia[27]. An agent considered by Dalldorf to be a Group B strain of Coxsackie virus ("Powers": Dalldorf, Group B, type 4) was implicated by Cheever and associates[7] in the etiology of an epidemic of "nonparalytic poliomyelitis" in Massachusetts in 1949, in which symptoms of pleurodynia were not described by the authors. However, a rise in antibody against this virus was demonstrated with paired serum specimens previously obtained from a patient with pleurodynia, and a virus stated to be identical with the "Powers" strain was subsequently associated with a large epidemic of pleurodynia in Holland[49]. The diverse illnesses observed by Kilbourne[28] to be associated with a Group B virus are compatible with the diagnosis of Bornholm disease or epidemic myalgia[52]. It is thus already apparent that the etiologic definition of "epidemic pleurodynia" is in remarkable accordance with case groupings on clinical grounds and substantiates inclusion of patients with varying symptomatology in this syndrome. That "pleurodynia" is an accurate designation for this illness is questionable, however, for as few as 23% of patients may have thoracic pain[32]. As pain is a symptom common to all patients[28], perhaps "epidemic myalgia"[37] will prove the most satisfactory clinical designation for this protean disease.

Evidence that the Coxsackie Viruses may be related to Human Disease: An examination of serologically proved instances of Coxsackie virus infection not obviously related to coincident poliomyelitis (Table 1).

In an assessment of the etiologic relationship of the Coxsackie viruses to human disease, the following factors must be considered:

1) Coxsackie viruses may be recovered from patients proved to be suffering from a disease of established viral etiology, for example, poliomyelitis[9, 12, 40, 48].

2) More than one strain of Coxsackie virus may simultaneously be recovered from the same patient[4].

3) Coincident specific antibody responses indicating simultaneous double infections with both Coxsackie and poliomyelitis viruses may occur in the same patient[39].

4) Coxsackie viruses may be carried by patients without disease[8], and clinically unapparent infections may occur[28]; the prevalence of normal carriers is unestablished.

5) There is no unequivocal evidence of the recovery of Coxsackie viruses from human tissue, and the pathologic anatomy of the human disease is unknown.

It is therefore suggested that a valid delineation of Coxsackie virus disease is possible only by analysis of cases fulfilling the following criteria:

1) Adequate clinical examination of the patient should be performed. The clinical syndrome should be one of previously undetermined or questionable etiology, not associated with or related to known pathogens.

2) Antibody response to a virus of the Coxsackie group should be demonstrated coincident with the patient's illness.

3) Virologic and particularly clinical evidence of poliomyelitis should be excluded.

4) Least important, but desirably, Coxsackie virus should be recovered from the patient.

SUMMARY OF DATA ON PATIENTS IN WHOM CLINICAL DISEASE HAS BEEN DEEMED AN

TABLE 1.

SUMMARY OF DATA ON PATIENTS IN WHOM CLINICAL DISEASE HAS BEEN DEFINED AND ANTIBODY RESPONSE AGAINST A COXSACKIE VIRUS HAS BEEN DEMONSTRATED, EXCEPTING PATIENTS WITH PROVED OR PROBABLE COINCIDENT POLIOMYELITIS.

Reference	No. of pts.	Age (yrs.)	Sex	Disease	Virus* recov.	Source	Virus strain	Dalldorf Classification	Antibody** response
Curnen *et al.*[10]	10	5-32	9M 1F	aseptic meningitis	5	stool	Conn 5	Group B, type 1	10
	1	?	M	pleurodynia	1	stool	Conn 5	Group B, type 1	none demonstrated
Kilbourne[28]	5	27-31	M	epidemic myalgia; diverse symptomatology	1	throat wash.	HK	Group B, type 1	5
Kilbourne[27]	1	13	M	epidemic myalgia	1	stool	DF	Group B, type (?)	1
Shaw *et al.*[50]	6	24-34	4M 2F	1) fever, sore throat, headache 2) pleurodynia 3) pleurodynia 4) malaise, headache, fever 5) sore throat, blurred vision 6) pleurodynia	6	stool (5) throat wash. (5)	1) Conn 5 2) Conn 5 3) Conn 5 4) Texas 5) Texas 6) Ohio	Group B, type 1 Group B, type 1 Group B, type 1 Group A, type 4 Group A, type 4 Group B, type 2	6
Weiler *et al.*[57]	7	13-26	?	epidemic pleurodynia	3	throat wash.	DeMole Kine McCarthy	? Group B, type 1 (like Conn 5)	7
Lazarus *et al.*[32]	4	?	?	epidemic pleurodynia	4	stool	.....	Group B, type 3	2
Huebner *et al.*[25]	1	35	M	headache, meningismus	1	stool sputum	.....	Group A, type 2	1
Huebner *et al.*[26] Beeman *et al.*[3]	19	<1-11	6M 13F	herpangina	19	stool and/or throat swab	H2,H2,H3 H4	Group A	19
Webb and Wolfe[55] (and Howitt)	1	6	F	"three-day fever"	1	throat wash.	.....	Group A, type 2	1
Findlay & Howard[19]	1	?	?	fever, thoracic pain (voluntary infection)	1	nasal wash., blood, stool	.....	Group B	

* No. of patients from whom virus was recovered.
** No. of patients in whom a significant antibody response was demonstrated.

It is obvious, of course, that none of these criteria may be satisfied with certainty. It is manifestly impossible to exclude the possibility of concurrent infection with multiple infectious agents in any patient; antibody response may not be demonstrable because of infection with a previously unrecognized Coxsackie virus strain not recoverable from the patient; poliomyelitis can never be definitely "excluded," either on clinical grounds or by failure to isolate virus; and Coxsackie virus may not be isolable from the patient under study. The criteria suggested may prove helpful, however, in future studies and may serve to emphasize present difficulties in the delineation of Coxsackie virus disease. Relatively few case reports in the literature satisfy these criteria (Table 1). Because of the present equivocal relationship of poliomyelitis and Coxsackie virus disease, even well studied cases of Coxsackie virus infection which occurred in temporal and geographic association with paralytic poliomyelitis have been arbitrarily excluded from this summary.

Of special interest are the infections of laboratory workers reported by Shaw and associates[50], because of the more direct evidence which they provide of the pathogenicity of Coxsackie virus for man. In these patients, in whom the possibility of other disease is remote, the symptomatology bears scrutiny. Symptoms typical of naturally occurring pleurodynia were observed in 3 to 6 patients studied; from each of these 3 a Group B strain of Coxsackie virus was recovered. Other patients suffered the more nonspecific complaints of malaise, headache and sore throat. Disease in all was benign, uncomplicated, and nonparalytic, although pleocytosis of the spinal fluid was found in one patient with pleurodynia.

From the relatively meager evidence thus far available, the following characterization of Coxsackie virus disease may be *tentatively* advanced, more as a guide to future investigation than as a definitive analysis:

Human illness associated with Coxsackie virus infection occurs in epidemic form, usually in late summer, and is probably world-wide in distribution. Disease may be manifest as epidemic myalgia or pleurodynia, as aseptic meningitis or "nonparalytic poliomyelitis," or as herpangina or "three-day fever." Unless associated with poliomyelitis, illnesses thus far have proved brief, benign, and without recognized sequelae or complications. Patients with pleurodynia or aseptic meningitis have been shown to be infected with strains of Coxsackie virus which may induce lesions of the nervous system in mice (Dalldorf, Group B), whereas herpangina has been associated chiefly with viral strains exclusively myotropic for mice (Dalldorf, Group A).

In future studies of the characterization of Coxsackie virus disease the clinician will play a paramount role. As Coxsackie viruses may be carried by those without manifest disease[8], and nonapparent infections demonstrated by antibody response may occur[17], the affirmation of the *fact* of disease and the *clinical nature* of the disease is as essential to the diagnosis of Coxsackie virus disease as are laboratory studies. The legacy of accurate clinical descriptions left by physicians of the past has already aided in the etiologic definition of both herpangina and epidemic pleurodynia.

In conclusion, it must be emphasized, as indicated by Godman and associates[21], that the Coxsackie viruses may not prove to be a true family of viruses but rather may include several unrelated viruses. Designation of

illness as "Coxsackie virus disease" would therefore appear unwise unless specific identification is made of the infecting strain of virus, for future investigations may well result in the separation and reclassification of the heterogeneous collection of viruses now termed "Coxsackie virus."

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PSYCHIATRIC ASPECTS OF SEXUAL DISTURBANCES

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THE dysfunctions that frequently arise in association with sexuality are not new. Earliest records clearly indicate that through the ages, mankind has recognized and has attempted to alleviate these problems.

We have all read in history and legend, of the aphrodisiac and the incantation, used in centuries past, to try to help those with sexual difficulties.

Modern medicine has utilized a more rational approach to attempt a clearer understanding of the sexual disturbances.

More recently we have come to recognize that some of these problems such as impotence and vaginismus, occasionally display organic or physiologic etiology. Others, like homosexuality, exhibitionism and voyeurism, are more obviously associated with psychogenic factors. However, even in those cases exhibiting some sexual difficulty, which are known to be due exclusively to some organic lesion, one may easily see the tremendous impact on the personality resulting from the disorder.

Countless men and women go through life, suffering needlessly because they are unable to confide their troubles to their family physicians. We deplore their necessity to remain silent, but when some of them, in their quest for help, consult their doctors, all too frequently many of us are at a loss for words, are unable to give the help asked for, and may dismiss the patient with a few platitudinous sentences.

The purpose of this paper is to review the psychiatric features of some of the sexual disturbances frequently seen by the general practitioner. Little space will be devoted to the so-called perversions, since these are more frequently dealt with by the psychiatrist.

Frigidity. Frigidity in women is the most common sexual dysfunction. Various investigators have determined that more than 50% of adult women are unable to obtain sexual gratification[33]. Many other women not only derive little or no pleasure, but actually experience pain and revulsion at the time of the sexual act.

Frigidity can only be related to ovarian function in the rare cases of ovarian agenesis or severe hypogonadism. Other rare organic causes for frigidity may be found in certain ill-

nesses of the central nervous system. Thus, we are able to recognize that this defect may be due to tabes dorsalis, poliomyelitis, multiple sclerosis and others. One may also accept the fact that severe acute emotional and physical stress due to exhaustion from overwork, toxic and debilitating disease, acute grief reactions in mourning, and others, may temporarily reduce or abolish the sexual appetite. In the vast majority of cases, however, a woman may be in excellent physical health, able to conceive and bear children, and still be the subject of any degree of frigidity.

Most of the classifications of frigidity are based on relative degrees of severity[23,33]. Thus, one may recognize the type of case with only occasional failure to achieve orgasm; and at the other extreme, cases of vaginal anesthesia with aversion to coitus.

THEORIES OF ORGASM. As the growing child begins to investigate herself, clitoral manipulation forms an early method of sexual expression. This type of masturbation results in the so-called clitoral orgasm. Many investigators feel that this gives way to "vaginal" orgasm in adult life. Bergler[3] refers to this in explaining frigidity. He believes that while clitoral orgasm may occur, frigid women never experience vaginal orgasm. Kinsey[16] and others doubt that one is able to distinguish clitoral from vaginal orgasm, basing his belief on the fact that the vaginal wall is very sparse in sensory nerve-endings. Freud[9] felt that if there were a transfer of sensations from clitoris to vagina, it was emotionally and unconsciously determined, and that this psychological transmission of sensations to the vagina did not occur in frigid women.

PSYCHOGENIC FACTORS IN FRIGIDITY[1,18,33]. 1. *Fear of Disapproval or Punishment.* Due to unfortunate attitudes regarding sexual pleasure, especially prevalent in the recent Victorian Era, the child often grows up feeling that there is something degrading about sex. He has been taught that the enjoyment of sexuality is not proper. A fear of ridicule or even a fear of actual physical punishment may result. This may be a carry-over from the time when the child actually was punished or ridiculed for masturbating or indulging in preliminary sexual play with other children. Thus, some women are uneasy about sexuality because of their fears of parental disapproval.

Occasionally these inhibiting factors are intensified when the young couple lives with the parents. The proximity of the punitive parents makes it difficult for some of these women to feel free from the old prohibitions. In many cases this type of frigidity is alleviated when the couple is advised to move out of the parents' home. In other cases the fears and prohibitions are so strong that psychotherapy is needed to resolve them.

2. *Fear of Pregnancy.* When the fear of pregnancy is so intense that actual frigidity develops, one should recognize that there are probably more deep-seated neurotic feelings centered around impregnation, pregnancy or labor. However, when the physician is able to evaluate that the fears are realistic and due to economic or other reasons, he may find that appropriate contraceptive advice will cause this form of "frigidity" to subside.

3. *Hostility Toward the Marital Partner.* This may be due to envy of the partner's role in life. A woman may resent what she feels is her domination by men. She may regard her femininity as a sign of weakness and be quite hostile to her husband who has relegated her to an inferior position as his "slave".

Another possibility is the woman whose relationships with her father or brother have been so unpleasant that she unconsciously transfers the hostility to her husband, and resents him in the role (which she has created for him) of father or brother substitute.

This unconscious resentment, for either of the above reasons, makes it extremely difficult for the woman to make her husband happy and "submit to him."

Many women are hostile to their husbands because they fear that they may be harmed by the penis. Weiss and English[33] report the case of the patient who stated, "each time I am faced with sex relations, I feel I am going to be pierced by a sword". To these women the sexual advance by the husband is a threatening and hostile gesture. They feel that if he is not doing something harmful he is at least performing upon them a degrading act, which he would not do if he really were a considerate person.

Less important, but present in some cases, is the woman's fear of harming the husband in some way by the sexual act. This fear may in fact be the conscious expression of an unconscious hostile desire and wish to harm the husband. At the root of some of the unconscious hostility is the old belief carried over from childhood that she was actually deprived of a penis in some way.

4. *Unconscious Conflicting Loves.* A woman who has never outgrown her early childhood love of her father or brother, may marry a man who reminds her of her father and then discover that she is frigid. In this case the frigidity is due to the fact that the woman may fantasy herself having intercourse with her father or brother, which of course, is prohibited. Thus, sexual relations are fraught with unconscious and conscious panic. This is an example of the so-called unresolved "Electra complex." Psychiatric case-histories are replete with patients having this type of difficulty.

Some cases of frigidity are due to latent homosexuality. Most of the patient's interests and emotional satisfaction lie in associations with her own sex, and sexual relations with a person of the opposite sex are at best only partially meaningful.

Other patients, those with very strong narcissistic drives, are so full of self-love that there just isn't enough love left over for another person. These people are very neurotic indeed, and needless to say, often represent difficult treatment problems.

It is obvious that much of the frigidity seen, will be noted to occur in women with other neurotic behavior. As Pinsky[27] has stated, "Frigidity is just one manifestation, one aspect of the patient's character disturbance." Thus, among frigid women we may note the aggressive champion for women's rights, the hostile grasping female, and the fanatic leaders and champions of virginity. Many spend their entire lives in violent constant competition with men. Also, frequently seen is the professional "gold-digger" who earns her living by exploiting men. Other cases try to escape their sexual dissatisfaction by compensatory interest in clubs, clothes or obsessive interest in their children and homes.

The patients who are capable of achieving orgasm but who fail to obtain gratification (due to ignorance on the part of the husband or his inability to satisfy the realistic sexual needs of his wife) frequently suffer from anxiety and multiple vague gynecologic complaints.

Gillett[11] recently investigated and interviewed 151 women who were not obtaining sexual gratification. Many of these woman placed the blame directly

on their husbands. They stated that they felt tense and unwilling to "give" (even though they were capable of orgasm) whenever they were unhappy due to unkindness, impatience, thoughtlessness, selfishness, or other fault on the part of their husbands. Some of these wives bitterly resented their continual unfavorable comparison to their husbands' mothers and sisters. Others claimed that for them marriage had become a "snare and a delusion", when they realized that they had been married for their money or for convenience. This author[11] states that one cannot separate a normal sex life from total emotional and family life. She notes that decrease of vaginal secretions is much more marked after a quarrel than after a hard day's work and fatigue. Gillett asks that the practitioner recognize the absence of organic and psychic pathology in these women, and concludes that many cases of sexual dissatisfaction are in fact "normal" frigidity, due not to psychologic defect in the wife, but actually caused by the husband.

Dyspareunia and Vaginismus. When not due to some obvious defect, such as an imperforate hymen, this may be regarded as an extreme form of psychogenic frigidity. Lack of sexual excitement is frequently associated with sparse secretions, which may result in painful intercourse. It may also be profitably noted here that decreased secretions in some cases may be due to excessive douching. In other cases, however, aversion to and fear of the sexual act may cause an involuntary contraction of the outlet muscles, rendering intercourse difficult and painful, or impossible. It is apparent that operations designed to enlarge the outlet in these latter subjects may result in severe psychic damage, since one has now taken away the patient's last defense against the hated and feared act. It should be remembered that vaginismus may occur not only in the virgin but also in multiparous women; and further, that many of these women may consciously desire intercourse, and not be able to recognize that their difficulties are caused by unconscious fears or hates.

Malleson[21] believes that in many cases of vaginismus, the patient had experienced pelvic pain of some kind as a child. Thus the patient equates the memory of the infantile fear of a painful rectal examination with the fact of vaginal penile entry.

Nymphomania. Contrary to the beliefs of many, the woman who suffers from nymphomania is not a highly sexed person at all. These unfortunate people rarely experience satisfactory orgasm, and may spend their entire lives in an inevitably fruitless search for sexual satisfaction. Hence, these cases may also properly be considered as another form of frigidity.

Diagnosis of Psychogenic Frigidity. The following points may be of some aid in the diagnosis:[19]

A. The physical examination should be negative. However, even if minor anomalies are found, great care must be exercised in evaluating their importance.

B. By kind and careful interviewing, the presence of emotional problems may be elicited. Discussion with and about the husband often proves very profitable. Occasionally, women will be encountered who seem quite relaxed and happy despite their frigidity. These may be considered to be, in many instances, representative of the cases to whom sexuality is so threatening that once having made an adjustment on a frigid level, they are quite content. These women are usually deeply neurotic and their prognosis is poor. When lack of sexual satisfaction results in emotional sequelae,

the prognosis may be considered to be much better.

C. The feminine orgasm, when complete, is characterized at its height by involuntary contractions of the pelvic and perineal musculature. These cannot be simulated and their presence or absence, and intensity may be determined by inquiry. In this way some insight may be gained by the physician as to the degree or severity of the frigidity.

D. Evidence of decreased vaginal secretions is another presumptive sign of frigidity. It should be noted, however, that the converse is not true. Adequate vaginal secretions do not necessarily mean that sexual satisfaction is being obtained. Many women have constant excessive leukorrhea, which may mask as the lubricating secretions noted in sexual excitement.

Sterility. Physicians have, for many years, been aware that the emotions are, in some way, associated with many failures of conception[25,29]. Rubenstein[29] noted a diminished fertility in psychotics. Cases are recorded[14] where conception occurred after psychotherapy. Countless stories have been told of the childless couples who were able to conceive shortly after adopting children[25]. Many doctors advise their patients that they will have better success if they wouldn't "try so hard." Hanson and Rock[12], however, on the basis of questionnaire material, were unable to verify this impression, that adoption can influence the ability to conceive.

In spite of this work, which has been criticized by many, it has become generally accepted[2,7] that the physiology of the female sexual organs may be altered profoundly by emotional disturbances. Many investigations have taken place and several theories proposed, as to how psychogenic sterility occurs. Some investigators[10,15,24] postulate that ovulation may be influenced by endocrine variations which can occur with hypothalamic or pineal stimulation upon the pituitary gland. The hypothalamus has long been suspected as the area upon which the emotions play so as to alter bodily functions. Autonomic imbalance, causing tubal spasm[28,30] has been invoked as another possible cause. Rubin[28] has shown repeatedly that tubal spasm is a frequent cause of sterility. It has also been well demonstrated that emotionally upset people reveal tremendous alteration in autonomic nervous system functioning. Tubal spasm responds to anti-spasmodics, and in many cases, to psychotherapy.

Psychodynamic Factors in Sterility. Repudiation of pregnancy, for any one of several reasons, is often at the root of cases of "psychogenic" sterility.

To an aggressive woman, striving toward masculinity, pregnancy is rejected because it typifies femininity. Many of these people frequently have important careers which they are unable to give up for the responsibility of taking care of a child.

Deep-seated hostility toward a husband may also be responsible for failure to conceive. These women are frequently able to become pregnant following psychotherapy or a more suitable remarriage.

Fear of the physical discomfort and pain associated with pregnancy and labor may also result in an inability to become pregnant.

Some neurotic, emotionally immature women unconsciously regard their marriages as father-daughter relationships. In cases such as these, pregnancy becomes very threatening and dangerous, because it may upset the precarious balance of this abnormal relationship.

Helene Deutsch[6] noted that strong guilt feelings, with their accompanying tensions, may be seen in some sterile women. Often in these cases expiation of their guilt feelings may release their tensions. Thus we hear of the cases who become pregnant after a severe economic blow. Deutsch states, that in some women, sterility subsides under physical treatment because these women may unconsciously interpret the treatment as punishment.

The psychiatric study of sterility is a relatively new field. Further investigations will undoubtedly bring more material to light and will surely help many more of these people to conceive children. Many more questions remain unanswered. As an example, is it possible that autonomic imbalance may also be responsible (as a result of inner tensions) in some cases of miscarriages and premature labor? Can a woman actually "reject the pregnancy" by autonomic influences upon the uterine musculature? This and other fascinating ideas must await future denial or confirmation.

Impotence[1,31,32,33]. Impotence in men is the counterpart of frigidity in women and is somewhat less common. Strauss[31] reports that 40% of married males complain of some degree of disability associated with the sexual act.

As was the case for frigidity, one may arbitrarily classify impotence according to relative severity. Some cases will reveal only occasional lack of pleasure in coitus, with no decrease in the ability to have an erection. Other men report that, although their interest and desire for coitus is maintained, they are not always successful in obtaining an erection. Sometimes the erection is inadequate or subsides too quickly. Frequently, we hear of cases where ejaculation is premature (ejaculatio praecox), or retarded (ejaculatio retardata). Many others complain of complete impotence in the face of sustained interest. Finally, there are those in whom neither the desire nor the ability is present.

Impotence, unlike frigidity, is more likely to wound a man's pride, more likely to lower his feelings of self-esteem. Since time immemorial, man has prided himself on his "virility." Frigidity in women, however, until quite recently in our culture, was regarded as a normal state of affairs.

After one has eliminated the patients whose difficulties are on an organic basis, a large number of cases remain whose problems are based on emotional disturbances. Most studies [31,32] indicate that over 90% of impotence is psychologically determined.

Psychogenic Factors in Impotence. Impotence and frigidity may both be regarded as protection against the person's own threatening emotions. Frequently, after initial causes have resulted in an inability to perform, succeeding attempts are fraught with shame and apprehension of further failure. The anxiety thus aroused often aggravates the degree of failure.

Often, on the wedding night, the bridegroom is tired, excited, and a little apprehensive. He may, on that occasion, discover to his great embarrassment, that he is unable to have an erection, or that ejaculation occurs before or during penetration. However, if the patient is a normal, healthy adult, not tortured or concerned with neurotic fears, this type of "impotence" proves to be temporary, and usually subsides as the partners adjust to each other.

Fear that the wife may become pregnant, may in some instances, cause inhibition and impotence. Here again, the physician should evaluate whether the fear is neurotic or realistic.

Another frequent temporary form of impotence occurs during emotional or physical exhaustion. This should carefully be differentiated from the patient who uses fatigue as a rationalization to explain his impotence, which may in fact be due to deep-seated inhibitions.

Occasionally, cases are seen which are derivatives of anxiety over masturbation and early sexual curiosity. Two forms may be identified. One is the man who unconsciously punishes himself by being impotent. His need for punishment arises from his guilt over masturbating. Another derivative is the man who fears ridicule or punishment if he has intercourse. This unconscious fear stems from the time that he was harshly ridiculed by punitive parents regarding his early sexual curiosity.

Temporary anger or deep-seated hostility toward the wife may render a man impotent. One result of hostility may be the unconscious desire to harm the woman. The conscious reaction to this may be a fear of harming the wife. Another effect of hostility is the husband's unwillingness to give the wife pleasure. This type of case often reports that he is able to have intercourse only with women other than his wife.

Seeking satisfaction outside the marriage may not necessarily, however, be due to hostility. The husband may have been brought up to regard sex as degrading, and, loving his wife does not want to "degrade her" by having intercourse with her. Hence, he seeks sexual pleasure with prostitutes.

Incestuous conflicts are found in another large group. If the man, because of his emotional immaturity, regards his wife as a mother or sister substitute, intercourse with her may be unconsciously equated as coitus with mother or sister, and hence forbidden.

Latent homosexuality and narcissism, discussed in the section on frigidity, may again be mentioned briefly as causes of impotence that will require no further elaboration at this time.

Premature and retarded ejaculation are merely forms of impotence and, although they are thought to have specific psychological meanings *per se*[1], their ultimate causes are those of impotence in general, and are hence dismissed without further discussion.

The Sexual Deviations[4,8,13,20,22,26-31]. It has long been thought by many that the man who resembled a woman and acted in an effeminate way, was frequently a homosexual. Similarly, Lesbians are frequently thought of as rather masculine in their actions and appearance. This led to the theory that there was a hormonal basis for homosexuality. Perloff[26] however, denies that hormones play anything more than a secondary role in sexual deviations, and goes on to state that "homosexuality is a purely psychological phenomenon, neither dependent upon a hormonal pattern for its production or amenable by endocrine substances to change". In addition to this it can be stated that homosexuals are frequently masculine in appearance, and Lesbians often quite feminine.

The sexual deviate whether he be zoophilic, transvestite, fetishist or homosexual, is an emotionally disturbed person, who relieves his tensions by distortions and displacements of his sexual outlets. Fenichel and others[4,8,13,20,22], regard "deviates" as people who have regressed to infantile levels of sexual expression, because adult sexuality is too threatening to them.

Blackman[4], in treating homosexuals noted a common feeling of isolation in these people. He reports that all of his cases revealed a childhood during which acceptance by a parent was

absent, status was denied, and the feeling of belonging to the family unit was not keenly present.

The sexual deviate is not born that way. Childhood experiences were largely responsible for the development of a neurosis affecting the entire personality, of which the patient's homosexuality or other disturbance is only one of the manifestations[13].

The perversions form a complex and difficult chapter in the therapeutic annals of psychiatry. London and Caprio[20] have collected the most recent material on this subject in book form, and present several detailed case histories.

Mayer[22] has noted that laws regarding sexual deviates vary widely. In some states only males are punished; in others, nudists may be convicted of being perverts. Some laws are lax, others very severe. (For example: In Colorado the maximum penalty for homosexuality is life imprisonment.)

Mayer asks the general practitioner to interest himself in the necessary legislation so that more intelligent laws regarding the deviate may be created.

In the above discussion, it may have been noted that most of the sexual disturbances are regarded as having their genesis in childhood. Colm's report[5] of sexual preoccupation in children as a reaction to parental disturbances and anxiety about sexual matters, is especially interesting in this regard. Since sexual difficulties seem to stem from childhood experiences, Knight's ideas[17] on their prevention may profitably be presented at this point.

1. There should be a good home atmosphere, absence of bickering before the children, and consistent affection and discipline by both parents to all the children.

2. It is important for parents not to influence a child of one sex toward the behavior appropriate to the other sex. This is very often seen in parents who were disappointed in the sex of their child.

3. Stories of how difficult their birth was, and how the mother almost died, should never be told to children, especially girls, who quite aside from feeling guilty about having caused such pain to the parent, may also develop a great fear of their own future pregnancies.

4. An unembarrassed attitude regarding bathing, toilet training, masturbation and sexual curiosity should prevail. It is probably wise to allow children of opposite sexes to witness each other in the nude while bathing, before the tenth year of life. Sexual questions should be answered correctly when they arise, and in an unembarrassed way, since children may pay more attention to the tone of voice and attitude than they do to the actual words.

5. Children should not sleep in the parents' room. Hearing the sounds of coitus or witnessing the act may be very frightening since it is often interpreted as an aggressive act.

6. Mothers should prepare girls for the onset of menstruation by unemotional explanation of its purpose.

7. Excessive warnings of chastity and of the "beast-like" quality of men may inhibit the young girl greatly in her later social relationships.

The study of sexual disturbances has only recently been removed from the shroud of shame, mystery and bias in which it has been cloaked. Many patients may be helped by kind straightforward discussion of the problem, and truthful reassurance. Some of the emotional disturbances that cause these problems are not apparent to the patient who is only aware that he is "anxious or nervous". In these cases the physician will have to evaluate whether he is going to undertake the

psychotherapy of the case himself, or whether he wants to refer the patient. Often, a private discussion between practitioner and psychiatrist about a given case will give the practitioner leads and cues on how to do his own treatment. The frigid women and impotent men were not born with their difficulty: it is possible for them to be helped.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MAY 20, 1952

Studies on Cerebral Physiology of Monkeys at 12 Negative G. T. D. DUANE, M.D., Ph.D., R. L. WECHSLER, M.D., J. E. ZIEGLER, M.D., and E. L. BECKMAN, M.D. (Aviation Medical Acceleration Laboratory, USN, Johnsville, Pennsylvania, and Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania.) A survey of the effects of repeated exposures to 12 negative G for 40 seconds was carried out on the monkey, and his response to this imposed stress evaluated. Cerebral circulation was measured by recording the passage of fluorescein through cortical vessels with the use of a photofluorometer attached to a cranial lucite window previously placed in the monkey's skull. Respiration was recorded via a thermocouple within the tracheal cannula. A quantitative measurement of the blood gases was performed upon blood withdrawn from the cerebral circulation during maximum G; electroencephalographic and electrocardiographic recordings were obtained by several methods; and the vascular pressure gradient across the brain was measured by pressure transducers in the carotid artery and in the confluens sinuum. Whenever possible, all recordings were made concurrently.

At 12 negative G for 40 seconds there was evidence of continuing cerebral circulation, apnea with secondary arterial anoxemia, and a lowering of the cerebral venous oxygen content suggesting cerebral anoxia. A transient enhancement of the electrical activity of the cortex was followed by gradual depression of varying degrees. The arterial and venous pressures were elevated, but their A-V gradient decreased severely during stress. Cardiac irregularities occurred with abnormally high T waves suggestive of severe cardiac anoxia. A failure of the cerebral venous oxygen content to return to the prerun level 10 minutes after deceleration indicates either an abnormality of cerebral metabolism or a decreased cerebral blood flow.

Thyroid Function and Surgical Trauma, as Evaluated by Iodine Conversion Ratio. H. C. BLOUNT, JR., and J. D. HARDY (Depts. Radiol. and Surgery, Hosp. U. Pa.) The iodine conversion ratio is a study in which the protein bound iodine in the blood serum is compared with the total serum iodine. There is general agreement that the rate of conversion of I_{131} into protein bound iodine in the plasma is a reliable measure of the function of the thyroid gland. (Hardy, J. D., Riegel, C., and Erisman, E.: Am. J. Med. Sci., **219**, 581, 1950.)

Because of an apparent increase in thyroid activity in some patients following operative procedures, excluding procedures on the thyroid gland itself, we have done radioactive iodine thyroid uptake studies and iodine conversion ratios in 14 patients before and approximately one week after various surgical procedures. Seven of these cases showed an increase of more than 10% in the conversion ratio in the postoperative study; 4 showed decreases of similar magnitudes after operation; and changes after operation were insignificant in the 3 remaining cases. Of

those patients having both I_{131} tracer studies and increased conversion ratios after operation, all showed increased thyroid uptakes of I_{131} in the postoperative studies. Those showing a decrease in conversion ratio, however, failed to show definite changes in the thyroid uptake of radioactive iodine. Control studies done in 8 persons on whom no surgery was performed showed definite increases in the conversion ratio in 3 cases in the second study, definite decreases in 3 cases, and 2 failed to show a detectable change in the second study. The results, though not significant, seem to indicate increased thyroid activity after surgery, at least in some cases.

The Diverse Physiological Responses in Man to Three Vasodilator Drugs, C-5, SKF 1700-A, and Ba-9295. By H. L. NEEDLEMAN, B.S., O. HORWITZ, M.D., and H. MONTGOMERY, M.D. (Peripheral Vascular Sec., Robinette Found., Hosp. Univ. of Penna.). The 3 vasodilator drugs mentioned above were studied for their immediate effects upon digital cutaneous blood flow, blood pressure, cardiac output and pulse rate. The peripheral blood flow was derived from digital skin temperature, the cardiac output from ballistocardiographic data, and the blood pressure was measured by the Riva Rocci method. The experiments were conducted in a constant temperature room maintained at 23± 1°C. The drugs were administered intravenously after a control period during which steady readings were established with respect to the above determinations. All 3 drugs usually caused vasodilatation in one or another part of the circulation.

Fifteen to fifty milligrams of C-5, a ganglionic blocking agent, administered to 14 subjects, increased the digital cutaneous blood flow in 9, but only after precipitous falls of the blood pressure, as much as 60 mm. Hg systolic and diastolic. The cardiac output was consistently but variably increased.

Five to fifteen milligrams of SKF-1700-A, a suprifen derivative of epinephrine, administered to 9 subjects, caused no measurable digital cutaneous vasodilatation, increased the pulse rate and cardiac output markedly and caused variable changes in the blood pressure in both directions. This indicates vasodilatation elsewhere than the skin. Arrhythmias and undesirable sympathomimetic effects were common.

Fifty to eighty-five milligrams of Ba-9295, another ganglionic blocking agent similar chemically to C-5, administered to 10 subjects, increased the digital cutaneous blood flow in 8 instances. This was accompanied by little change in blood pressure, pulse rate and cardiac output. No undesirable side effects were noted.

The intravenous trials of these drugs confirm the usefulness of C-5 as a hypotensive agent, and suggest a therapeutic use for Ba-9295 as a peripheral vasodilator.

The Concentration of Magnesium Ion in Serum and Ultrafiltrates of Serum and the Magnesium-Binding Property of the Serum Proteins. F. WILLIAM SUNDERMAN, B. E. COPELAND and M. J. WILLIS. (Division of Metabolic Research, Jefferson Medical College, Phila.) The present studies were undertaken to demonstrate the partition of magnesium into diffusible and non-diffusible moieties in normal human serum, and to determine the magnesium binding-power of the serum protein fractions, albumin and globulin. Measurements were made of magnesium in serum and ultrafiltrates of serum, and of nitrogen and magnesium

in the protein fractions. All concentrations were calculated on a water basis.

It was shown that magnesium proteinate acts as a slightly soluble salt, according to the mass law relationship. A dissociation constant for this relationship was calculated in 17 samples of normal human sera and the $pK_{Mg\ Prot}$ was found to be 1.77 s.d. 0.15. An equation was derived by which Mg^{++} could be calculated from the (1) dissociation constant, (2) total serum protein; and (3) total serum magnesium. A high degree of correlation was demonstrated between the calculated M^{++} and the measured M^{++}.

The magnesium-binding power of serum albumin was estimated to be 0.0128 ± 0.004 m.Eq. per gram albumin. The magnesium-binding power of serum globulin was estimated to be 0.0081 ± 0.003 m.Eq. per gram globulin.

BOOK REVIEWS AND NOTICES

SERUM SICKNESS. By C. FRH. VON PIRQUET, M.D., and BELA SCHICK, M.D. Translated by BELA SCHICK, M.D. Pp. 130; 31 ills. Baltimore: Williams & Wilkins Co., 1951. Price, $3.50.

THIS is a translation of the book, "Die Serumkrankheit" that was an important landmark in the beginnings of our knowledge of the field of human hypersensitiveness. The translator, Doctor Schick, was junior author of the original work and today is a recognized and outstanding leader in this field of medicine. All students of allergy owe Doctor Schick a debt of gratitude for providing them with this excellent translation of a medical classic. R. K.

ELECTROCARDIOGRAPHIC STUDIES IN NORMAL INFANTS AND CHILDREN. By ROBERT F. ZIEGLER, M.D., Associate in Cardiology in charge of Section of Pediatric Cardiology, Henry Ford Hospital, Detroit. Pp. 207. Springfield, Ill.: Charles C Thomas, 1951. Price, $10.50.

IT is axiomatic that, in order to accurately diagnose abnormalities, one must be aware of what constitutes normality. And yet, in the field of pediatric cardiology, many an opinion of electrocardiographic abnormality has been rendered without sufficient cognizance of the range of findings within the bounds of what may be considered essential normality in infancy and childhood. In fact, complete standards of electrocardiographic normality for these age groups have not been available up to the present. There have been, of course, many reports concerning various intervals and deflections in the standard leads, but data relative to the extremity potentials and precordial derivations are largely lacking. Dr. Ziegler's magnificent study was aimed at the establishment of complete standards, and at a critical interpretation of the data obtained in terms of current concepts of electrocardiography. He has succeeded admirably in this. The data are based on studies of two series of children ranging in age from birth to 16 years. The first series included 250 children on whom standard unipolar and extremity leads were made, the precordial leads being excluded because of technical error. In the second series of 300 children, complete electrocardigrams were made. The author is to be congratulated on the completion of so large a work in such a splendid manner. The book will prove to be of great service to all who are involved in pediatric cardiology. T. D.

STANDARD NOMENCLATURE OF DISEASES AND OPERATIONS. Edited by RICHARD J. PLUNKETT, M.D., and ADALINE C. HAYDEN, R. R. L. 4th ed. Pp. 1,034; 4 ills. Philadelphia: The Blakiston Co., 1952. Price, $8.00.

NEARLY ten years have passed since the last edition of this very important publication. A large number of collaborators, representing many fields of medicine, have worked over a period of several years to bring this edition up-to-date. The reviewer regrets, however, that no allergist was included among the revisers and so the deficiencies in this field continue. For example, nasal mucous polyp, a recognized allergic end result, is still listed under diseases due to unknown cause. The new edition will be welcomed by all medical librarians and its use in all hospital record rooms is heartily recommended. R. K.

DISEASES IN OLD AGE. A Clinical and Pathological Study of 7941 Individuals over 61 years of Age. By ROBERT T. MONROE, M.D. Pp. 402. Cambridge, Mass.: Harvard University Press, 1951. Price, $5.00.

As stated in the subtitle this book gives a survey of disease in the elderly based on nearly 8,000 records over a 30-year period (1913-1943) from a teaching institution where excellent work is documented in good records. The patients were not institutionalized individuals but represent samples of their age group in the community. The material has been well-digested and the discussion of the data is excellently written and there are many useful tables. The author also offers some excellent suggestions from the standpoint of future needs, medical, social and institutional, in the care and treatment of the aged, based on his own experience in a geriatric clinic. There are some gaps in the material. All cases were selected from admissions to the medical service. There are no data on patients from the surgical wards. There is nothing on peripheral vascular disease and there are no data on smoking and its prevalence or possible effects. Clinicians will find this a very interesting and useful book. R. K.

KLINIK UND THERAPIE DER VERGIFTUNGEN. By DR. SVEN MOESCHLIN. Pp. 430; 53 ills. Stuttgart: Georg Thieme Verlag (Grune & Stratton, American distributors), 1952. Price, DM 45.

THIS is an excellent book on the clinical aspects of the various poisonings. The tremendous development of the chemical industry in recent years has brought about the introduction of many new toxic substances in industry as well as in pharmacology. The present volume covers an unusually wide range in the field of toxicology. The presentation is concise and orderly, supplemented by helpful illustrations and references to the literature throughout the world. The book is highly recommended to those who read German. R. K.

CURRENT THERAPY, 1951. Edited by HOWARD F. CONN, M.D., Pp. 699. Philadelphia: W. B. Saunders Co., 1951. Price, $10.00.

AN augmented staff of contributors and careful editorial supervision are responsible for this excellent compilation of what is new and good in therapeutics. The discussions are brief, practical, and to the point. In order to cover the field, it has apparently been necessary to conserve space with a resultant oversimplification at times, and omission of some items (various things that give rise to food poisoning offer an example). The book will be welcomed by practitioners as a valuable work for quick reference. R. K.

HEREDITY IN UTERINE CANCER. By DOUGLAS P. MURPHY, M.D., F.A.C.S., Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania. Pp. 128. Cambridge, Mass.: Harvard University Press, 1952. Price, $2.50.

THE author attempts to determine the role of heredity in uterine cancer. The study is based on the occurrence of cancer among the relatives of 201 women with proved cancer of the uterine cervix, as compared with that in 215 control families. In all, 6,445 individuals were investigated. The methods and materials used in this study are described in detail. The results of comparable studies made elsewhere are reviewed. The statistical analysis is presented with clarity, indeed the entire report could serve as a model of technique in this difficult field. Although the study deals primarily with the familial occurrence of uterine cancer, the incidence of cancer in any part of the body is considered. The principal conclusion reached by the author is that hereditary factors affect the frequency with which cancer appears in the uterus, but the quantitative effect is small. P. K.

PROGRESS IN ALLERGY, VOLUME III. Edited by PAUL KALLOS. Pp. 572; 82 ills; 1 colored plate. New York: Interscience Publishers, Inc., (American agents for S. Karger, Basle, Switzerland), 1952. Price, $16.25.

THIS volume contains chapters on various aspects of clinical allergy. The writers are recognized authorities in their several fields not only in this country but abroad. Subjects covered include Allergy in Children, Bronchial Asthma Due to Food Allergy, Infective Factor in Asthma and Rhinitis, Cardiovascular Allergy, Chemical Investigations on Ergot Alkaloids, Autonomic Nervous System and Ergot Alkaloids in Allergy, Ergot Derivatives in the Treatment of Migraine, Drug Allergy and Sedormid Purpura, all in English. There is one chapter in German on Pneumometry. The presentations place emphasis on clinical aspects. R. K.

SIGNS AND SYMPTOMS. By CYRIL MITCHELL MACBRYDE, M.D., F.A.C.P., Assoc. Prof. Clin. Med., Washington Univ. School of Med., St. Louis. 2nd ed. Pp. 783; 98 ills. Philadelphia: J. B. Lippincott Co., 1952. Price, $10.00.

THE appearance of the second edition within five years of the first is testimony to the value of this work to the practicing physician in the diagnosis of disease. Patients present signs and symptoms, not diagnoses. This volume offers practical information on the mechanisms by which the various signs and symptoms are produced. The 26 contributors are not only recognized authorities in their several fields but have teaching experience and proved ability to transmit their knowledge. The edition includes new chapters on Pathologic Bleeding, Skin Pigmentation, Vertigo, and Hypertrophic Osteoarthroplasty. Each chapter is well documented with references. The illustrations are well done and the format is good. Practitioners of medicine will find this a useful volume on their desks. R. K.

CHILD PSYCHIATRIC TECHNIQUES. By LAURETTA BENDER, M.D. Pp. 335; 55 ills. Springfield, Illinois: Charles C Thomas, 1952. Price, $8.50.

DR. BENDER has attempted to review the major areas of the psychiatric treatment of

children in this volume. She begins with an excellent summary of the development and schools of thought regarding therapy of emotionally disturbed children. A section is included on the Child Guidance Movement, the American School of Child Psychotherapy, as well as Educational Psychology and Behaviorism. Various projective techniques, including art, music, dancing, play with toys and dramatic play, have been discussed and considerable time is devoted to the principles of Gestalt psychology. Later, Dr. Bender describes, with case histories, the general handling of activities and therapy on a Children's Ward. The reader is then introduced to the various techniques involved in treating disturbed children in a psychiatric ward, with special emphasis on art and dancing, as well as other methods. Many of Paul Schilder's contributions are mentioned and discussed. We have found this book to be interesting reading, filled with clinical examples and most worthwhile material, especially for the person involved with in-patient care and treatment of defective and disturbed children. S. F.

TEXTBOOK OF CLINICAL PARASITOLOGY. By DAVID L. BELDING, M.D., Prof. Bact. and Exp. Path., Emeritus, Boston University School of Med. 2nd ed. Pp. 1139; 283 ills. New York: Appleton-Century-Crofts, Inc., 1952. Price, $12.00.

EXPERIENCES during and after World War II have been productive of rapid and extensive advances in the field of Parasitology. As a result, the second edition of this useful textbook includes much new material. The mode of presentation is excellent, with many tables, graphs and good illustrations that greatly facilitate the accessibility of the material. It would be particularly helpful to medical officers of the Armed Forces and Public Health Service and to laboratory workers. The clarity and orderliness of presentation also recommend its use in the teaching of Parasitology. R. K.

THE PATHOGENESIS OF TUBERCULOSIS. By ARNOLD R. RICH, M.D., Baxley Professor of Pathology, Johns Hopkins School of Medicine. 2nd ed. Pp. 1,028; 105 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $15.00.

WHEN the first edition appeared in 1944 it immediately became the most useful book in the field of tuberculosis. Those persons already familiar with the first edition will find no extensive revision of content or point of view but will notice the incorporation of literature through 1950. Delay in publication explains why no reference is made to such subjects as the adrenal cortical hormones.

For those who do not know this book it can be said that Doctor Rich has produced a literary tool of inestimable value. Having selected 1500 references as representing the present state of knowledge, he proceeds in a comprehensive, lucid and persuasive manner to describe his concept of the pathogenesis of tuberculosis. The reader may not always agree with the author's interpretation of published data or opinions derived from them, but there is never any doubt as to where Doctor Rich stands. Therein lies the stimulating influence of this book. By defining so sharply those areas in which confusion is due to lack of knowledge he has contributed significantly to the progress of research.

The publisher is also to be congratulated upon the physical quality and attractiveness of the volume, noticeably better than that of the earlier edition. E. S.

PATHOLOGY OF THE FETUS AND THE NEWBORN. By EDITH L. POTTER, M.D., PH.D. Pp. 574; 601 ills., Chicago: Year Book Publishers, 1952. Price, $19.00.

For a good many years there has been need of a book devoted to the pathology of the fetus and newborn. The recent tendency to consider pediatric pathology a subspecialty has intensified this need. Doctor Potter has supplied the long-awaited volume and in doing so has produced a very fine book. She has deftly summarized what has been published in this field and added the conclusions of her own vast experience at the Chicago Lying-in and other hospitals. The result is a concise but surprisingly complete work which few pathologists or pediatricians can now afford to be without. She sticks closely to her subject and whereas twenty-nine pages may seem, to some, too few for the discussion of tumors she wisely treats only the tumors characteristic of the period, assuming, I suppose, that there are other sources for tumors of later decades which only rarely affect the newborn. On the other hand, she devotes thirty-one pages to the pathology of the placenta and cord, material which is difficult or impossible to find elsewhere, and in the treatment of the diseases which are found only during this particular period, resorption atelectasis with hyaline membrane,

kernicterus and infantile cirrhosis, to name a few, she is thorough. The volume is profusely illustrated. The bibliographical lists are adequate. E. A.

CALLANDER'S SURGICAL ANATOMY. By BARRY J. ANSON, M.A., PH.D. (MED.SC.), Professor of Anatomy, Northwestern University Medical School, and WALTER G. MADDOCK, M.D., F.A.C.S., Elcock Professor of Surgery, Northwestern University Medical School, 3d ed. Pp. 1074; 929 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $14.00.

THE new edition of Callander's Surgical Anatomy, which was completed by Drs. Anson and Maddock as the result of Dr. Callander's untimely death, has retained the original pattern of previous editions. The book contains, in addition to the surgical anatomy of the various portions of the body, a large amount of fundamental clinical medicine and surgery. The illustrations are taken from a multitude of sources and are generally excellent ones. The type is clear and readable and the paper is of satisfactory quality.

The book is recommended as a reference text for medical students and should be a part of the library of all surgical interns, surgical residents and general surgeons.

H. C.

ANTIBIOTIC THERAPY. By HENRY WELCH, PH.D., and CHARLES N. LEWIS, M.D., Director and Medical Officer, respectively, Division of Antibiotics, Food and Drug Administration, Washington, D. C. Pp. 562, 35 graphs. Washington, D. C.: The Arundel Press, Inc., 1951. Price, $10.00.

THIS volume differs from the earlier ones on this subject by including all the important antibiotics, by its textbook structure and its authoritative tone. The last characteristic is to be expected inasmuch as the authors are charged with certification of antibiotics under the Federal Food, Drug and Cosmetic Act. They could easily have compiled a mere compendium of the reported information and let it go at that. Because they did not do so makes this an important book.

There are three main divisions: (1) historical development of each antibiotic currently on the market or with a reasonable prospect of reaching it; (2) antimicrobial spectrum, pharmacology and dosage forms; (3) clinical experience in the treatment of the most common infectious diseases. The style is clear and concise, the selection of content good. Although this book is not a complete reference for antibiotics, it is destined to be the standard one.

Physicians will find the unbiased evaluation of many competing commercial products helpful and refreshing. In spite of an inadequate index, this is still a "must" book.

E. S.

INCONTINENCE IN OLD PEOPLE. By JOHN C. BROCKLEHURST, M.D. Foreword by Stanley Alstead, M.D., F.R.C.P. Pp. 191; 62 ills. Edinburgh: E. & S. Livingstone Ltd., 1951. Price, $6.50.

THIS monograph is an attempt to correlate the known facts and factors producing incontinence in the aged. A review of pertinent facts as recorded in the literature is given. The etiology of incontinence in its varying forms is discussed. The management of incontinence by various drugs, rehabilitation, and by appliances is presented.

The use of the molded bed in the management of the conditions is also presented. Several types of construction are discussed, although the proper construction of such a bed is not suggested.

This book fails to contribute any worthwhile knowledge to that which is already known. L. M.

HISTORY OF MEDICINE IN IRELAND. By JOHN FLEETWOOD, M.B., D.P.H. Pp. 420; ills. Dublin: The Richview Press, Browne and Nolan, 1951. Price, 21 sh. ($2.94).

READERS interested in the earlier and more qualitative side of Ireland's medical history will find the first 4 chapters—through the Renaissance—of chief interest. Here a pronouncing glossary would have been helpful. Many will be surprised at the antiquity of Irish medicine and its closely parallel course with medical progress in England and the Continent. The later chapters tracing the growth of schools, hospitals and societies into the 20th Century become more and more statements of unconnected facts, useful "for the record" but not attracting the general medical reader. The book, which is not intended to be "an exhaustive account of Irish medical practice throughout the centuries," satisfactorily presents outstanding events and personalities. The 3 page chronological list (extending from 1000 BC to 1949), and the classified Bibliography of 16 pages add considerably to the value of the book on one's shelves. E. K.

NEW BOOKS

Fluid Balance. By CARL A. MOYER, M.D., Professor of Surgery, Washington University School of Medicine. Pp. 191; Fig. 3. Chicago: The Year Book Publishers, Inc., 1952. Price $3.75.

In this small volume there is to be found a thorough and detailed discussion of the diagnosis and management of the common types of fluid and electrolyte abnormalities encountered by the surgeon. Excellent descriptions of the clinical and laboratory findings in various states of fluid imbalance and specific directions for their correction are included. The author enhances its value by citing numerous case reports from his broad experience. C.S.

Kreislaufuntersuchungen am Menschen mit Fortlaufend Registrierenden Methoden. By K. MATTHEW, Professor of Internal Medicine, Erlangen. Pp. 326; 205 ills. Stuttgart: Georg Thieme Verlag, 1951. Price, DM 48.

THIS excellent book in German deals chiefly with methods developed by the author himself. The techniques of others are only briefly mentioned. The results included cover the experiences of over fifteen years. The experiments show the reactions of the vascular system of normal man under various conditions. Pathology is included only a few times. The following sections are included: methods, arterial oxygen, oxygen saturation and vascular reactions after artificial occlusion of the arterial circulation, photometer readings of volume pulse, rhythmic variations of blood pressure and pulse in man, vasomotor reflexes, hyperventilation and carbondioxide respiration, oxygen lack, effect of work on the circulation, Cheyne-Stokes respiration, and a section on pharmacology. The illustrations are especially good. This book also contains a bibliography of 409 references. Workers in this field should find this book useful. M.O.

Recommendations for Waste Disposal of Phosphorus-32 and Iodine-131 for Medical Users. U. S. Department of Commerce, National Bureau of Standards Handbook 49. Pp. 14; 2 ills. Washington, D. C.: U. S. Department of Commerce, 1952. Price, $.15.

THIS pamphlet comprises the most authoritative and carefully thought out guide to the disposal of radioisotopes thus far available, and constitutes the temporary authority on this subject. R.R.

The Medical Works of Hippocrates. By JOHN CHADWICK, M.A., Sometime Scholar of Corpus Christi College, Cambridge, and W. N. MANN, M.D., F.R.C.P., Assistant Physician to Guy's Hospital. Pp. 301. Springfield, Illinois: Charles C Thomas, 1951. Price, $5.50.

Methods in Medical Research. By M. B. VISSCHER, Editor-in-Chief. Pp. 306; illustrated. Chicago: Year Book Publishers, Inc., 1951. Price, $7.00.

Grouping, Typing and Banking of Blood. By OTAKER JAROSLAV POLLAK, M.D., Ph.D., Director, School for Medical Technologists, Quincy City Hospital, Quincy, Mass. Pp. 163; 25 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $5.75.

Bacterial Physiology. By C. H. WERKMAN, Department of Bacteriology, Iowa State College and P. W. WILSON, Department of Biochemistry, University of Wisconsin. Pp. 707; 20 ills. New York: Academic Press, Inc., 1951. Price, $8.50.

Two of America's outstanding bacterial physiologists have produced an advanced text which will be the standard reference in its field for years to come. Each chapter is in effect an authoritative and critical review. The all too common and wearisome method of recording experimental results has uniformly been replaced by a refreshing emphasis upon the broad significance of observed facts.

Medical investigators and teachers especially concerned with antiseptics, bacterial genetics and chemotherapy will find in this volume much reliable and important information. E. S.

Prescription for Medical Writing. By EDWIN P. JORDAN, M.D., and W. C. SHEPARD. Pp. 112; 26 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $2.50.

A concise, clear and practical statement of the basic principles of good medical writing. This involves not only composition, titling, bibliography, index, and illustrations but also some tests to establish the validity of statistics. Even the most experienced medical writer can find some helpful suggestions in this excellent little book.

R. K.

Liver Disease. A Ciba Foundation Symposium. Edited by SHEILA SHERLOCK, M.D., and G. E. W. WOLSTENHOLME, B. CH. Pp. 249; 112 ills. Philadelphia: The Blakiston Co., 1951. Price, $5.00.

THIS book contains contributions on recent advances in investigation of liver disease by outstanding research workers from America and Europe. Fundamental and clinical aspects of protein metabolism, cirrhosis, portal hypertension, ascites, pigment metabolism, hepatic blood flow and hepatitis are reported and discussed in an informal but provocative manner. The ability of the contributors to simplify complex subjects while presenting them in a concise, pithy fashion, makes reading of this book both entertaining and rewarding.

S. L.

Proceedings of the 3rd International Congress of the International Society of Hematology. Edited by CARL V. MOORE, M.D. Pp. 593; illustrated. New York: Grune & Stratton, 1951. Price, $10.00 (cloth); $8.00 (paper).

NEW EDITIONS

A Textbook of Clinical Neurology. By ISRAEL S. WECHSLER, M.D., Clinical Professor of Neurology, Columbia University, New York, N. Y. 7th ed. Pp. 801; 179 ills. Philadelphia and London: W. B. Saunders Company, 1952. Price, $9.50.

THIS is the seventh edition of an excellent textbook of neurology by an eminent and outstanding clinical neurologist. As before, the book is very well suited for use by the medical student and the busy practicing physician. The revision was perhaps overdue (last edition 1947). The new material includes electromyography briefly discussed. Retained, and appropriately so, are the discussions of psychologic diagnosis, the neuroses and the history of neurology.

S. G.

Essentials of Histology. By MARGARET M. HOSKINS, Ph.D. and GERRIT BEVELANDER, Ph.D., New York University. 2d ed. Pp. 240; 135 ills. and 2 color plates. St. Louis: C. V. Mosby Co., 1952. Price, $4.00.

THE fundamental morphological characteristics of the tissues and organs of the body are discussed in the usual order of presentation of most of the older and larger textbooks of histology. The authors' treatment is concise, clearly presented, and well illustrated. One error was noted, however, in that the authors, failing to distinguish clearly between renal sinus and renal pelvis, state that the lumen of the ureter is continuous with the renal sinus (page 163, lines 4 & 5).

While this volume is obviously presented as an elementary textbook it might be a distinct aid to many freshmen medical students—especially if utilized with slides at the microscope. Also any clinician who desires to review normal histology in preparation for the pathological portion of certain of the post-graduate Board Examinations will find this little book most valuable.

N. B.

The Physician as Man of Letters, Science and Action. By THOMAS K. MONRO, M.A., M.D., LL.D., Emeritus Regius Professor of Practice of Medicine, University of Glasgow. 2d. ed. Pp. 259. Baltimore: Williams & Wilkins Company, 1951. Price, $4.50.

SOME 18 years ago, the author first published collected data relative to medical men who had distinguished themselves in ways other than the practice of medicine. The present work contains about one-third more biographical sketches than did the earlier edition, the increase being due to the inclusion of individuals previously overlooked and also to recent deaths of distinguished persons. There are included no living individuals. Although the sketches are necessarily brief, they are interesting and informative. One learns, for example, that it was a physician who coined the term "John Bull." "In Flanders Field," "Thesaurus of English Words and Phrases," "Sorrell and Son," "The Adventures of Sherlock Holmes," and "Hugh Wynne, Free Quaker," are but a few of the literary endeavors of medical men. Philosophy, politics, music, piracy, and crime are some of the other categories to which physicians have made notable contributions.

Those interested in history in general, as well as the history of medicine, will find this a refreshing volume.

C. Z.

Diagnostic Bacteriology. By ISABELLE G. SCHAUB, A.B., Technical Director, Clinical Bacteriology Laboratories, The Johns Hopkins Hospital, and M. KATHLEEN FOLEY, M.A., Instructor in Bacteriology, Department of Biological Sciences, College of Notre Dame of Maryland, Baltimore, Maryland. 4th ed. Pp. 356. St. Louis: C. V. Mosby Co., 1952. Price, $4.50.

THE previous edition of this book was generally acknowledged as the leader among laboratory guides devoted exclusively to bacteriology. Significant changes in the new edition, all of which are definite improvements, raise its stature even further. There is more text material explaining the principles which govern selection and usefulness of laboratory procedures, and more discussions directed toward the interpretation of results. The authors are to be congratulated for accomplishing this without loss of the outline guide arrangement of the previous edition. Incorporation of new procedures such as antibiotic susceptibility tests, combined with intelligent choice of available methods, brings this volume completely up-to-date and makes it a "must" for all workers in diagnostic bacteriology. E.S.

Recent Advances in Bacteriology. By J. H. DIBLE, M.B., F.R.C.P., Professor of Pathology, Postgraduate School of London, Editor; J. D. MACLENNAN, M.B.E., M.D., Research Associate, Columbia University, and MARY BARBEE, M.D., Reader in Bacteriology, St. Thomas's Hospital Medical School. 3rd ed. Pp. 325; 14 ills. Philadelphia: The Blakiston Co., 1951. Price, $5.00.

THE latest edition of this well known book has a place in all reference libraries. In it are contained some of the best brief reviews available anywhere of such important subjects as bacterial morphology, bacterial synthesis of vitamins in the intestine, antigenic structure of streptococci and the paracolon bacilli. Especially valuable, however, is the extensive discussion of anaerobic infections, a topic to which 40% of the text is devoted and about which Doctor MacLennan can write authoritatively. This is not a textbook and the authors should give up any pretense that it is. This volume can be used effectively if the reader first notes the relatively few subjects dealt with and then refers to it whenever he needs a quick review of one of them. E. S.

Hypertension. A Manual for Patients with High Blood Pressure. By IRVINE H. PAGE, M.D., Director, Research Division, Cleveland Clinic Foundation, Cleveland, Ohio. Revised 6th printing. Pp. 101; 7 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $3.00.